A STUDY TO PREDICT STENOSIS IN ESOPHAGEAL CANCER PATIENTS AFTER DEFINITIVE RADIATION THERAPY

DISSERTATION

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Certificate

This is to certify that the dissertation entitled "**A study to predict stenosis in esophageal cancer patients after definitive radiation therapy**" is a bona fide record of the original work done by **Dr. Venkata Krishna Reddy Pilaka** towards the partial fulfillment for the award of **Doctor of Medicine** in **Radiotherapy** of The Tamil Nadu, Dr. M.G.R Medical University, Chennai conducted in April 2014.

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Abstract

Introduction

Esophageal cancer has a poor prognosis. Multimodality approach with neoadjuvant chemoirradiation followed by surgery is the treatment of choice. For patients who are inoperable or refusing surgery, definitive chemoirradiation is the standard modality of treatment. At present, the survival rates of esophageal cancer are low and improving the quality of life is one of the aims of treatment. Dysphagia due to radiation induced stricture is one of the distressing complications of definitive radiation therapy in esophageal cancer patients which decreases the quality of life. This study addresses the incidence and risk factors for the development of strictures following radiation therapy and attempts to predict the formation of the same, which in turn may aid in selection of the best modality of treatment.

Aim

The study aims to find the incidence of esophageal stenosis and risk factors causing the stenosis following definitive radiation therapy. It also aims to formulize an equation for the prediction of esophageal stenosis based on the identified risk factors.

Methodology

This is both a prospective and retrospective observational study which included the data of esophageal cancer patients from January 2008 to July 2013. The study included 100 patients with locally advanced esophageal cancer who underwent definitive radiation therapy with or without chemotherapy. Esophageal stenosis was evaluated during the first follow up and three monthly thereafter by endoscope negotiability. This study investigated the correlation between esophageal stenosis after radiation therapy and risk factors related to tumour and treatment characteristics. For validation of the correlative factors for esophageal stenosis, boot strapping method was employed. A

formula was then derived to predict the esophageal stenosis following definitive radiation therapy.

Results

Out of the 100 patients, data for 72 patients, who came for follow up, were available for analysis. The incidence of stenosis after definitive radiation therapy was 43 % (31 out of 72 patients). On univariate analysis, esophageal stenosis was likely to occur if the patient had T4 stage of esophageal cancer, the endoscope not being negotiable prior to radiation therapy, and involvement of the entire circumference of esophageal wall. In multivariate analysis, T4 stage alone correlated significantly with stenosis of esophagus (p= 0.03). Bootstrapping analysis showed that T4 stage and the extent of circumference of esophageal wall involved were significant factors for predicting stenosis (OR -1.90 and 5.18 respectively). A derivational formula was thus arrived at to predict the esophageal stenosis.

Prediction equation = $\frac{e^{y}}{1+e^{y}}$, where

y = -4.1435+0.6356*staging-0.4674*scopnego+0.5340*length-0.0965*wallthick + 1.6455*circumference.

Conclusions

Our study suggests that T4 stage and the involvement of full circumference of the esophageal wall are significant risk factors for formation of esophageal stenosis following radiation therapy. The predictive formula which was derived from the derivative cohort needs to be validated prospectively in a larger sample of patients.

Keywords: Esophageal stenosis, Definitive radiation therapy, Esophageal Cancer

Aim of the Study

1. To find the incidence of esophageal stenosis after definitive radiation therapy
2. To identify the risk factors associated with the development of esophageal stenosis after definitive radiation therapy.
3. To formulize an equation for prediction of esophageal stenosis based on the identified risk factors.

Introduction

Esophageal cancer is the eighth most common cancer worldwide. It is more common in males, with male to female ratio of 3-5:1. The main symptoms with which esophageal cancer patients present with are dysphagia, weight loss, heart burn, odynophagia and shortness of breath. Of these symptoms, dysphagia is the main symptom responsible for decreasing the quality of life. The mortality rate among the esophageal cancer patients despite radical treatment is high. The two and five year overall survival rates are 24.3 % and 13.8 % respectively(1). As the overall survival rates in esophageal cancer patients are low, one of the main intent of treatment in these patients is improving the quality of life.

Esophageal cancer patients can be treated by surgery or non surgical techniques depending on the stage. Patients with early stage esophageal cancer, T1 and T2 lesions are best treated with surgery. Stages I to III, selected IVA are considered for curative resection, while IVB tumours are considered unresectable. Those tumours with doubtful invasion into the surrounding structures and those tumours which cannot get adequate margins after surgery are considered for neoadjuvant chemoirradiation followed by surgical excision. Those with locally advanced disease and who are considered unsuitable for surgery due to comorbid conditions are offered definitive chemoirradiation. Even with the combined modality treatment approaches, overall survival rates continue to be dismal. The mortality rates are high within the first two years(2). Although surgery has been the main modality of treatment, there is however,

no compelling evidence to show that survival rates are better in surgery group than in the definitive radiation therapy group (3).

As the survival rates are low with the available treatment modalities, improvement of quality of life remains to be one of the main aims of treatment. Definitive chemoirradiation is the option for patients who are considered unresectable or in those patients who refused surgery. Definitive chemoirradiation comprises of 45 Gy of external beam irradiation along with concurrent chemotherapy over a period of 5 weeks followed by two fractions of intraluminal high dose rate brachytherapy. The main complication of radical chemoirradiation is early esophageal stenosis, which is multifactorial either due to fibrosis or tumour regression. Esophageal stenosis reduces the quality of life in patients receiving radical radiation therapy. The causative factors responsible for esophageal stenosis after definitive chemoirradiation are higher tumour (T) stage (TNM classification), length of the esophagus involved, extent of involved circumference and also the wall thickness of esophagus at the time of treatment(4).

The quality of swallowing had been assessed in operable esophageal cancer patients who underwent surgery or definitive radiation therapy(5). This showed that surgery resulted in improvement of swallowing twice as much as in patients who received radiation therapy after correction for time and pretreatment swallowing status. Predicting esophageal stenosis prior to radiation therapy may aid the patient in selecting the treatment modality which may result in a lower risk of esophageal

stenosis, especially in a patient suitable for surgery, but is not keen to undergo surgery (5).

The proposed study is both a retrospective and prospective study, which assesses the stenosis after radiation therapy objectively with endoscopy and imaging modalities and correlates the same with the patient's symptoms. It will assess the patient's symptoms before and after radiation therapy and correlate the dysphagia with the risk factors. By knowing the risk factors prior to radiation therapy it is possible to select patients who will not develop symptomatic esophageal stenosis after radiation therapy.

There are limited studies for evaluating the frequency and severity of esophageal stenosis after radical chemoirradiation in esophageal cancer patients. This study will attempt to validate the risk factors which are causing esophageal stenosis and predicting the severity of stenosis caused because of tumour regression and radiation therapy based on those risk factors.

Literature review

Epidemiology

Oesophageal cancer is the eighth most common cause of cancer in the world accounting for 3.8 % of total estimated cancers in 2008. It is the sixth most common cause of death accounting for 5.4 % of total cancer patient deaths. Esophageal cancer is more common in males than females with male to female ratio of 3 to 5:1. In 2008, new esophageal cancer cases identified were 4, 82,300 and number of deaths which occurred due to esophageal cancer were 4, 06,800 globally. Highest rates were found in Southern and Eastern Africa and Eastern Asia. The highest risk area stretches from the northern Iran along the Central Asian republic to North-Central China. This is referred as esophageal cancer belt in which 90% of the cases are squamous cell carcinomas. Major risk factors for the high incidence of esophageal cancer in this belt are not clearly known. However, poor nutrition, drinking beverages at high temperatures, low intake of fruits are considered risk factors. Lower incidence is seen in United States and many Western countries. In Westren countries there is increased incidence of esophageal adenocarcinoma, which rose to greater than 300 to 500 % in the last 30 to 40 year period (6,7). However, the etiology of 90 % squamous cell carcinoma of esophagus in these countries constitutes smoking and alcohol (8).

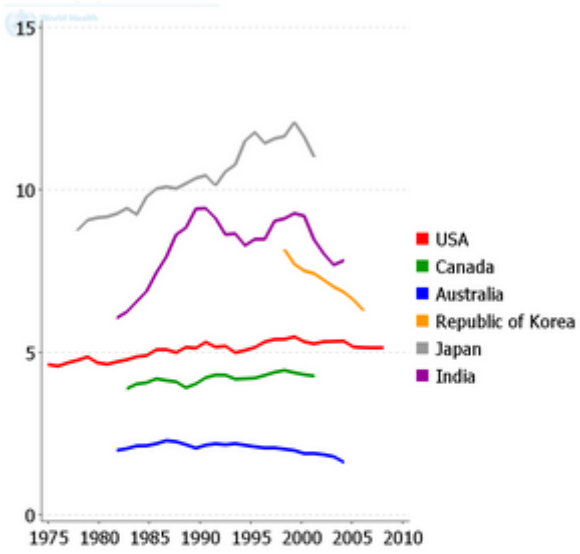
In India, incidence of esophageal cancer is moderately high. It is the fourth most common cancer among the males and ranks fifth among the females. According to the Indian population based cancer registries, the incidence of oesophageal cancer was

42,447 in 2001 and is projected to increase to 66,672 by 2016 (2). In India the estimated number of patients having esophageal cancer in the previous 5 years was 2,57,000 from 2008. According to International agency of research on cancer, India had 47,000 cases per year in 2008 and mortality of 42,000 patients per year (9).

According to Cancer Registry of Chennai, from 2006 to 2008, the incidence of esophageal cancer among males was 6.8 % and among females was 3.45 %. The crude rate of incidence of esophageal cancers per 1,00,000 population was 6.8 % among the males and 3.9 % among the female population. The age adjusted average annual incidence of esophageal cancer was 7.6 % among the males and 4.3 % among females. The mortality rate of esophageal cancer from 2006 to 2008 was 6.92 % among the male population and 4.9 % among the female population.(10)

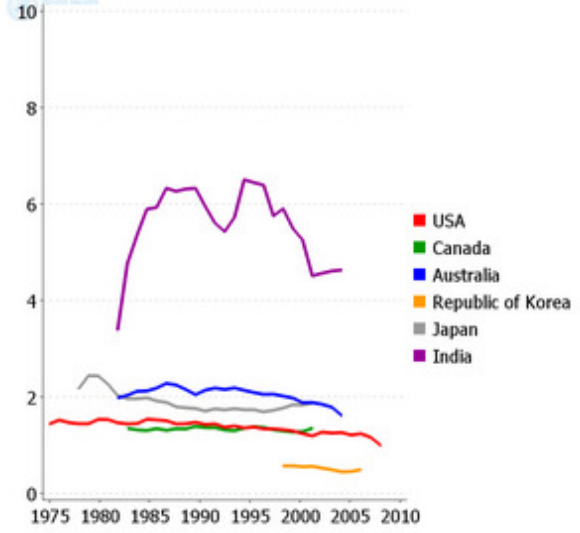
There are variations in the incidence of esophageal cancer according to histological subtypes. Incidence of adenocarcinoma of esophagus is mostly seen in Western countries due to obesity. The percentage of adults who are overweight has been increased in the population to greater than 33 %. The mechanism by which obesity predisposes to esophageal adenocarcinoma may be increased intraabdominal pressure and increased risk of of gastroesophageal reflux disease and progression to metaplasia of Barrett's esophagus(6). However, these countries have a reduced incidence of squamous cell carcinoma due to reduction in tobacco and alcohol consumption. Asian countries have higher incidence of squamous cell carcinomas of esophagus due to increased tobacco and alcohol consumption.(11)

Trends in incidence of oesophageal cancer in selected countries: age-standardised rate (W) per 100,000, men



Australia: www.aihw.gov.au
Canada: www.statcan.gc.ca
India: Chennai cancer registry
Japan: Miyagi, Osaka and Yamagata cancer registries
Republic of Korea: www.ncc.re.kr
USA: SEER program: seer.cancer.gov

Trends in incidence of oesophageal cancer in selected countries: age-standardised rate (W) per 100,000, women



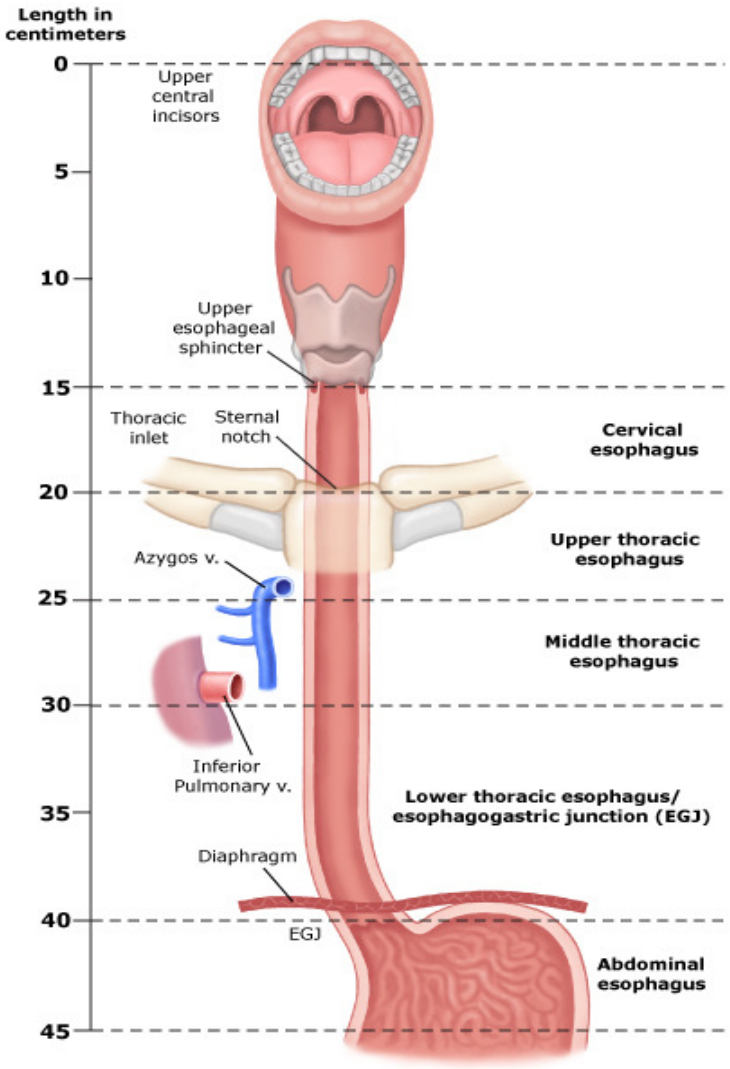
Australia: www.aihw.gov.au
Canada: www.statcan.gc.ca
India: Chennai cancer registry
Japan: Miyagi, Osaka and Yamagata cancer registries
Republic of Korea: www.ncc.re.kr
USA: SEER program: seer.cancer.gov

Oesophageal Cancer Incidence and Mortality Worldwide in 2008
Summary : GLOBOCAN 2008

Gross anatomy

The oesophagus is a muscular tube like organ starting from C6 vertebra after hypopharynx and extending to T11 region into stomach. It starts from the cricopharyngeus muscle till the gastro-esophageal junction. It is divided into cervical and thoracic esophagus. The thoracic esophagus is in turn divided into three parts:

upper, middle and lower third esophagus which is divided based on specific anatomical boundaries.



Anatomical division of Esophagus. In: AJCC Cancer Staging Manual, 7 th edition, 2010.

The length of the esophagus extends from 22 – 30 cm and it varies according to the age and gender. The cricopharyngeal region is around 14 to 15 cm from the incisor teeth and the gastroesophageal junction is 38 to 42 cm from the incisor teeth. The cervical

esophagus extends from 16 to 20 cm, i.e from cricopharyngeus muscle to thoracic inlet. The upper third esophagus extends from 20 to 25 cm, i.e from thoracic inlet to tracheal bifurcation. The middle third esophagus extends from 25 to 32 cm and lower third esophagus extends from 32 to 40 cm. The anatomical regions are important in decision making of treatment of esophageal cancer.(12)

Staging of esophageal cancer

The American Joint Committee on Cancer had proposed the TNM classification of carcinoma of esophagus. The staging is as follows according to the AJCC 7 th edition, 2010 :

Primary Tumor (T)

TX: Primary tumor cannot be assessed

T0: No evidence of primary tumor

Tis: High-grade dysplasia**

T1: Tumor invades lamina propria or submucosa

T1a: Invasion of lamina propria or muscularis mucosa

T1b: Invasion of submucosa

T2: Tumor invades muscularis propria

T3: Tumor invades adventitia

T4: Tumor invades adjacent structures

T4a: Resectable tumor invading pleura, pericardium, or diaphragm

T4b:Unresectable tumor invading other adjacent structures such as aorta, vertebral

body, trachea etc.

*At least maximal dimension of tumor must be recorded; multiple tumors require the T(m) suffix.

**High-grade dysplasia includes all noninvasive neoplastic epithelia that was formerly called carcinoma in situ, a diagnosis that is no longer used for columnar mucosa anywhere

in the gastrointestinal tract.

Regional Lymph Nodes (N)

NX: Regional lymph nodes cannot be assessed

N0: No regional lymph node metastasis

N1: Metastasis in 1-2 regional lymph nodes

N2: Metastasis in 3-6 regional lymph nodes

N3: Metastasis in seven or more regional lymph nodes

*Number must be recorded for total number of regional nodes sampled and total number of reported nodes with metastasis

Distant metastasis (M)

MX: distant metastasis cannot be assessed

M0: no distant metastasis

M1: distant metastasis

Physiology of swallowing

Swallowing or deglutition is act of swallowing, through which a food bolus is transported from the mouth through pharynx and esophagus into the stomach. Swallowing is divided into three phases, namely:

1. Oral
2. Pharyngeal
3. Esophageal

Of these three phases, the esophageal and pharyngeal phases of swallowing are vital to understand the effects of radiation on swallowing.

Pharyngeal phase:

The steps involved in pharyngeal phase of swallowing are:

1. Elevation of the soft palate to contact posterior pharyngeal wall preventing the regurgitation of food bolus into nasopharynx. This is also called velopharyngeal valving
2. Elevation of the larynx and hyoid bone towards the base of tongue causing flipping of epiglottis to cover glottis.
3. Pharyngeal muscle constriction from above to downward direction

4. Relaxation of the cricopharyngeal sphincter to allow the passage of food bolus into esophagus

The soft palate is elevated by the levator veli palatine muscles so that it comes in contact with the posterior pharyngeal wall and prevents the food from coming into the nose during swallowing.

During swallowing the important action is adduction of the vocal cord to protect the tracheal airway. This action occurs before the elevation of larynx and hyoid. After the adduction of true vocal cords, false vocal cords, aryepiglottic folds adduct and finally flipping of epiglottis to cover the glottis.

The epiglottis also helps in rolling of food bolus to pyriform sinuses. These areas are places where residual food bolus may accumulate and may result in aspiration. There will be a time period when no breathing happens during swallowing; however swallowing tends to occur in expiration.

Pharyngeal peristalsis takes place when true vocal cords adduct and this is evidenced by contraction of the pharyngeal constrictor muscles in superior-inferior order. When the superior constrictor is contracted, the larynx begins to elevate.

The food bolus then reaches the cervical region of esophagus.

Esophageal phase:

This phase starts when the bolus enters the esophagus. The bolus is carried through peristaltic movement until the lower esophageal sphincter. The lower esophageal sphincter opens to allow bolus into the stomach. The peristaltic movement requires the action of esophageal musculature. It creates a positive pressure in esophageal chamber to move bolus towards stomach. The lower esophageal sphincter closes once the food enters the stomach and cannot move back up into the esophagus.

Symptoms in Esophageal cancer patients

The five most frequent symptoms associated with esophageal cancer are dysphagia (74%), weight loss (57.3%), heart burn (20.5 %) odynophagia (16.6 %) and shortness of breath (12.1 %). The most common presenting symptom is esophageal cancer patients is dysphagia. Other symptoms and signs associated with esophageal cancer are cervical lymphadenopathy, chronic cough, hematemesis, hemoptysis, hoarseness of voice. Dysphagia is associated with other symptoms as a combination in 8 out of 10 patients. The most common combination of symptoms associated with dysphagia is weight loss. This is associated with poor quality of life of patient as well as it is a poor prognostic factor.(13)

Dysphagia is difficulty in having initiation of swallowing or a feeling that liquid or solid diet is getting obstructed in the passage from mouth to stomach. It is a perception of

that there is a hindrance in normal passage of food. Dysphagia can be due to oropharyngeal causes or due to esophageal causes.

Patients with esophageal cancers have varied range of swallowing difficulty from solids to liquids. However, most patients have difficulty in swallowing solids but not to liquids which is due to the mechanical obstruction with luminal narrowing to diameter less than 15 mm (3). If the esophageal cancer is left untreated, symptoms would progress causing absolute dysphagia. This causes marked weight loss because of poor intake. All these symptoms causes decrease in quality of life of patient.

Locally advanced esophageal cancer has poor prognosis and have 5 year survival rates of approximately 20 – 30 %. As the survival rates are poor, the primary aim of treatment in esophageal cancer patients is to improve the symptoms and quality of life along with intention to cure. Of all the symptoms, dysphagia need to be addressed with importance as it is the major contributing factor of decreasing the quality of life of patients.

Factors causing esophageal stenosis after radiation therapy

As briefly mentioned earlier, various factors play a role in causing stenosis after definitive chemoirradiation.

Very few studies were done which correlated esophageal stenosis with specific factors. Of the various factors, the important factors which were studied were age, gender, tumour stage, circumference of the esophagus involved, length of the tumour, wall

thickness of the tumour, site of the esophagus involved, dysphagia score before initiation of the treatment, stenotic level before the treatment, dose of radiation therapy, whether intraluminal radiation therapy was a component of the radiation course and whether concurrent chemotherapy was administered(4,14).

Age of the patient was not correlated with the esophageal stenosis. Studies were done where they had categorized patients either as above and below 60 years or above and below 70 years. But, they were not predictive of increased rates of stenosis in either group.

Male or female patients had same rate of stenosis rates and were only dependent on other factors. Gender had no significant correlation with esophageal stenosis after radiation therapy. However studies predicting esophageal stenosis after radiation therapy to head and neck cancers showed that females have more predilection to form stenosis(15).

Various stages of Esophageal Cancer (staged according to AJCC) have been correlated with esophageal stenosis after radiation therapy. The correlation of tumour stage and stenotic rates has been variable in literature. Some studies showed a significant increase in the rate of stenosis in higher stages i.e T4 whereas T2 and T3 tumours had stenotic rates almost half the rate of the T4 stage tumours(4). However, some studies have shown no difference in esophageal stenosis rates after definitive radiation therapy across various T stages.

Circumference of the esophagus involved at the time of diagnosis has a high degree of correlation with the esophageal stenosis after radiation therapy. It was studied whether or not whole circumference of esophagus was involved. Full circumference involvement of esophagus by the tumour was highly predictive of esophageal stenosis after radiation therapy.(4,16)

Length of the tumour in esophageal cancer at the time of diagnosis was studied for the prediction of esophageal stenosis. In some studies it was grouped into those greater than 5 cm and those less than 5 cm where as in others, it was grouped into greater than 8 cm or less than 8 cm. The results however were contradictory. Retrospective studies done by Atsumi et al which were analyzed by univariate and multivariate analysis showed variable results. In one of the studies, length of esophageal involvement by the tumour which was greater than 5 cm had correlation with esophageal stenosis after radiation therapy ($p = 0.005$) (16). A randomized trial showed 99 operable esophageal cancer patients were randomly allocated into surgery arm and radiotherapy arm based on age, T stage and length of esophageal involvement whether less than or greater than 5 cm and the quality of life was assessed which showed no significant difference either groups (5).

Esophageal wall thickness of the tumour region was strongly correlated with formation of stenosis after completion of radiation therapy. The patients were divided into subgroups of those having wall thickness of 1 cm and less and those with wall thickness greater than 1 cm. The latter group had significant increase in the incidence of

esophageal stenosis as compared with former group. The wall thickness of 1 cm and less had 0 to 2 % stenotic rates as compared to 32- 38 % in those having wall thickness of greater than 1 cm(4,16).

Site of involvement of esophageal cancer was not critically evaluated as factor for prediction of esophageal stenosis following definitive radiotherapy. Most of the studies done on esophageal cancer and radiation therapy involved middle third of esophagus. Study done by Khurana et al in 2007, showed no difference in the stenotic rates between upper, middle or lower third esophagus (14).

Dysphagia score at the initiation of treatment correlated with the severity of stenosis at the time of presentation. Dysphagia was scored based on the diet which the patient was able to eat i.e. whether patient could eat solid diet, soft & pureed food, liquid diet or nothing at all. The results were varied in various studies. The dysphagia grade did not correlate with the stenosis formation after radiation therapy. But the grade of stenosis before starting treatment had predicted the formation of stricture after radiation. The esophageal stenosis was grouped according to those who are having greater than 50 % lumen stenosed or those having less than 50 % of the lumen stenosed. Esophageal stricture formation was higher with patients having stenosis causing greater than 50 % of the lumen compromise before the initiation of the treatment (4).

Studies which correlated various dose regimens given as external beam radiation therapy to formation of esophageal stenosis were not significant. Study done by Atsumi et al had categorized patients into those who received dose less than or greater than 65

Gy, which did not show any difference in stenosis formation. However, in the next study he divided patients into those who received radiation dose greater than 65 Gy to the tumour bed and those receiving between 65 to 70 Gy and those who received greater than 70 Gy. In this study he showed those patients who received greater 70 Gy had higher stenotic rate formation after completion of the treatment (13 vs 13 vs 33 %) (16). However no specific dose limits for esophagus could be illustrated due to lack of published data. It is suggested from clinical data that 74 Gy could be safely administered to a segment of esophagus with concurrent chemotherapy (17).

Intraluminal brachytherapy (ILRT) following external beam radiation therapy is an important contributor for esophageal stenosis formation. It depends upon various factors like duration between ILRT and external beam radiation therapy, type of applicator used, dose fractionation, interval between two ILRT doses and total dose given. Stenotic rates were higher if the duration between external beam irradiation and ILRT was less than one week. If applicators of lesser than 1 cm in diameter is introduced for ILRT it causes higher rates of injury to esophagus and there by higher stenotic rates. If the applicator diameter was less than 2 mm the complication rates were 24 % as compared to 19 % with diameters of 2 to 6 mm and 5 % with those applicators having diameter greater than 6 mm. Those receiving less than 5 Gy had complication rate of 9.5 %, those receiving between 5 to 8 Gy had complication rate of 20 % and those receiving greater than 8 Gy had complication rates of 38 %. It was suggested that smaller fraction size should be used as far as possible with the total dose received by ILRT keeping at 10 to 12 Gy. (18). Shorter interfraction intervals of three to seven days

causes higher rates of stricture formation as compared to those greater than one week gap between the two fractions (14). The time to the formation of stricture after intraluminal radiation therapy was lesser when compared with those who received external beam radiation alone.

Concurrent chemotherapy when given along with radiation therapy was associated with higher incidence of stenotic formation after definitive chemoirradiation. Various chemotherapy regimens like weekly Cisplatin, 2 cycles of Cisplatin and 5 Flourouracil, 2 cycles of 5 –Flourouracil and Mitomycin, weekly Docetaxel, weekly Paclitaxel and Carboplatin have been tried as concurrent chemoirradiation. Concurrent chemotherapy when administered along with radiation therapy had higher incidence of stricture formation than those who did not receive (12 % in historical group vs 34 % in those who received chemoirradiation and ILRT) (14). Those who received both ILRT and concurrent chemotherapy with external beam radiation therapy had higher incidence of stricture formation than those who received external beam radiation and ILRT alone. The hazard ratio was 4.2 in concurrent chemoirradiation group as compared with those who did not receive chemotherapy. It was suggested that ILRT should be used with caution in those patients who are receiving chemotherapy.

With these factors as background which can affect the outcomes and complications after treatment of esophageal cancer, the present study concentrates on specific factors which will be dealt in detail in materials and methods section.

Patho-physiology of radiation induced esophageal strictures

The detailed mechanism by which esophageal stenosis occurs after radiation therapy are not known. However, fibrosis or ischemia occurring during radiation therapy are the main identified factors contributing to stenosis. The above mechanisms can happen during the tumour shrinkage also. Studies have shown that esophageal stenosis after radiation therapy to the neck and thorax region showed histological evidence of fibrosis of the sub-mucosa and hyalinization of the smooth muscle layers of the esophagus. This is followed by accumulation of macrophages which releases pro-inflammatory cytokines.(19) This causes thickening in the submucosa and muscular layers causing edema and fibrosis. The vascular damage and ischemia associated with esophageal stenosis after radiation therapy is less important. These processes occur more around the tumours which shrink and respond to radiation therapy. Esophageal stricture is a result of scarring or due to abnormal growth in the esophageal lumen. The involved circumference of esophagus shows greater co-relation with effects radiation therapy due to the above mechanisms explained. Similar process has been observed in patients who had undergone esophageal mucosal resection. Esophageal cancer patients who had underwent esophageal mucosal resection had a higher propensity for esophageal stenosis if two thirds to three fourths of the circumference of the esophageal mucosa was removed (16).

In order to predict the risk factors, the patho-physiology of radiation induced esophageal stenosis is important. Circumference of esophagus wall involved and the wall thickness might help in prediction of esophageal stenosis following definitive chemoirradiation.

Treatment protocols for esophageal cancer and the complications associated with them

Survival rates of esophageal cancer have remained low; however the outcomes of the resectable loco-regional disease have improved with multimodality treatment, which include radiation, chemotherapy and surgery. The symptoms associated with esophageal cancer occur when the disease is fairly advanced. Most of the patients are therefore diagnosed at late stages (3). As there is a paucity of large randomized trials, treatment decisions are based on either small randomized trials or meta-analyses. Treatment of esophageal cancers is one the difficult challenges for surgeons, radiation oncologists and medical oncologists.

For early esophageal cancer patients with stages cT1 – T2 N0 disease, surgery alone remains the standard of care for this local disease. There is little evidence which supports the use of radiation or chemoirradiation as definitive treatment in patients with T1N0 disease. A small study which treated patients who refused surgery into external beam radiation therapy alone (64 Gy) or external beam (52 Gy) followed by 8 to 12 Gy of brachytherapy. The 5 year survival rates were 59 %. However, patients with

T2N0 stage, require adjuvant radiation therapy after radical esophagectomy as they have 50 % propensity for lymph node metastases (20,21).

There is controversy for current standard of care for patients with locally advanced esophageal cancer (cT3-T4 and or N positive). Until 1980s, surgical resection was the main modality of treatment. In 1980s, perioperative chemotherapy, postoperative chemoirradiation and preoperative chemoirradiation have found to improve the outcomes. These studies had limitations like inadequate power, type of chemotherapy used, dose of chemotherapy, radiation dose and fractionation, radiation delivery schedules, initial staging and histological subtypes (22).

Various queries still persist about the benefits of neoadjuvant radiation, peri-operative chemotherapy, concurrent chemoirradiation, surgery and neoadjuvant chemoirradiation followed by surgery and also on adjuvant treatment after surgery. The ideal treatment for esophageal malignancy is still not defined.

Phase III studies which have evaluated neoadjuvant radiation showed improved 5 year overall survival rates but these were not statistically significant. The use of radiation as single modality in neoadjuvant setting for esophageal cancer is not supported by current literature (23).

Phase III trials comparing surgery alone with neoadjuvant chemotherapy alone have shown a survival advantage. Medical Research Council trial is the largest one which showed 5 year overall survival advantage of 6 % in esophageal adenocarcinoma and squamous cell carcinoma. MAGIC trial and the French Cooperative Group had

demonstrated 5 year overall survival advantage of 13 % and 14 % which consisted predominately gastric cancer patients. As subsequent studies had shown neoadjuvant chemoirradiation to be superior in esophageal cancer, the use of preoperative chemotherapy has diminished.

Chemoirradiation is used both in neoadjuvant setting for esophageal cancer patients or in the adjuvant setting for patients with gastro-esophageal junction tumours. It may be used as definitive treatment in patients who are not fit for surgery. These decisions should ideally be made in a multidisciplinary tumour board setting. RTOG-85-01 trial evaluated definitive treatment in patients with esophageal squamous cell carcinoma who were not surgically fit. It showed a 5 year over all survival of 27 % in patients who received chemoirradiation as compared to 0 % with radiation alone. But the locoregional failure was 47 %(24). INT 0123 trial addressed the issue of optimum dose of radiation. It randomized patients to high dose (68.4 Gy) or low dose radiation (50.4 Gy) and it failed to show that a high radiation dose has an increase in local control or survival benefit.

FFCD 9201 study randomized patients into definitive chemoirradiation and those with neoadjuvant chemoirradiation followed by surgery. This showed that patients who underwent neoadjuvant chemoirradiation followed by surgery had low rates of local recurrence (24 %) as compared to chemoirradiation alone (46 %), however overall survival rates at 2 and 5 years did not show statistical difference. The patients who underwent surgery had lesser need for palliative treatment for dysphagia as compared

to patients who underwent chemoirradiation alone. Study conducted by Stahl et al in 2005, which compared definitive chemoirradiation and neoadjuvant chemoirradaition followed by surgery, showed no difference in the overall survival in both groups, but there was improved locoregional control in the patient who underwent surgery. This study showed that patients who had clinical tumour response after neoadjuvant treatment showed to have improved overall survival.(2,25,26) The CROSS study which randomized operable esophageal cancer patients to surgery alone and preoperative chemoirradiation followed by surgery which showed statistically significant improved overall survival in the later group (27). Based on these studies, combined modality with chemoirradiation and surgery has now become the standard of care as it improved locoregional control.

Many centers use intraluminal brachytherapy in addition to the external beam radiation to escalate the radiation dose in a select group of patients. In ILRT, esophagus is accessed by a catheter based system and radiation source is used to treat esophageal tumours while sparing the normal surrounding structures. ABS guidelines recommends intraluminal brachytherapy in treatment of esophagus in two settings; a) as definitive treatment in esophageal cancer where there is mucosal involvement of esophageal mucosal wall only and b) as palliative intent in those patients whose life expectancy is less than 6 months. It divides the patients into good candidates, poor candidates and in those whom ILRT is contraindicated. Good candidates are those in whom the tumours are less than 10 cm in length, tumours confined to esophageal wall only, thoracic esophagus involvement and no lymphadenopathy. Poor candidates are those with

tumours involving more 10 cm of the esophageal length, peri-esophageal extension, tumour involving gastroesophageal junction or cardia and positive lymphadenopathy. Patients in whom ILRT is contraindicated are presence of esophageal fistula, cervical esophageal involvement and in those patients who are having stenosis of esophagus which cannot be bypassed (28). There are two types of brachytherapy a) High Dose Rate (HDR brachytherapy in which the dose rates are above 12 Gy per hour and b) Low Dose Rate (LDR) brachytherapy in which dose rates are below 2 Gy per hour. Various dose schedules have been in tried in both HDR and LDR brachytherapy. The RTOG 92-07 study showed that survival did not improve with addition of intraluminal brachytherapy to definitive chemoirradiation with increase in treatment related fistulas in brachytherapy group. It expresses an extreme caution while giving ILRT following external beam irradiation(29,30). Although various schedules have been tried, ABS recommends HDR brachytherapy dose as 10 Gy in 2 fractions, 1-2 weeks after completion of external beam irradiation, one week apart and LDR dose as 20 Gy given 2-3 weeks after completion of the EBRT. The coverage volume is 1-2 cm proximal and distal to primary tumour and the dose prescribed to 1 cm from the source(28). Two prospective studies showed improved survival when EBRT was combined with ILRT as compared with EBRT alone. Sur et al randomized patients who are treated with 35 Gy/15 #/ 3 weeks to group A who received EBRT dose of 20 Gy/10 #/2 weeks and group B who received ILRT dose of 12 Gy/2 sessions/2weeks. They found that group B had higher actuarial survival rates (44% in group A vs 78 % in group B) and relief of dysphagia at the end of one year (37.5% in group A vs 70.6% in group B) (31). Several retrospective studies have shown

benefit of local control. Although survival did not improve as compared with EBRT alone groups, the local control and survival were found to be strongly correlated (32). But the largest study was done in Japan with esophageal brachytherapy which randomized patients to EBRT and HDR brachytherapy and EBRT alone showed improvement in 2 year local control rate with no improvement in survival (33). There is clear evidence to say that ILRT increases the risk of late complications (esophageal stenosis, broncho-esophageal fistulas). However, a retrospective trial conducted by Khurana et al showed that there was a threefold increase in late complications following ILRT. Only large prospective clinical trials needs to address the benefit of adding brachytherapy boost to external beam irradiation of esophageal cancer.

Surgery plays an important role in treatment of patients with esophageal cancer. Earlier studies showed that non-surgical approach was not associated with good results and that surgical approaches had better survival rates but with high rates of complications. There are three approaches for esophagectomy : a) transhiatal b)transthoracic and c) enbloc or radical. Two meta-analyses done in 2001 and 2011 showed no difference in survival comparing transhiatal and transthoracic approaches (34,35). In the present era, different studies showed the rate of mortality close to zero in patients with non – advanced or even advanced tumours. Patients with potentially resectable tumour have lower survival rates if not undergoing surgery. The survival of the patient after surgery depends on many factors like initial disease status, neoadjuvant and adjuvant treatment received and does not depend on surgery alone.

This raises the question whether patients benefit from neoadjuvant chemoirradiation. Numerous studies were done with various doses and fraction sizes of radiation, variety of chemotherapy regimens and timing of chemotherapy and radiation. Of which 3 studies had shown benefit with neoadjuvant concurrent chemoirradiation. The CALGB 9781 trial which randomized patients to cisplatin and infusional 5 Flourouracil with concurrent radiation and surgery to surgery alone showed an five year overall survival of 39 % in combined modality as compared to 16 % with surgery alone. Similar study by Walsh et al showed 3 year overall survival of 32 % in multimodality treatment and 6 % in surgery alone arm. Two meta-analyses showed a statistically significant benefit with neoadjuvant chemoirradiation when compared to surgery alone (36). The CROSS study which randomized operable esophageal cancer patients to surgery alone and preoperative chemoirradiation followed by surgery which showed statistically significant improved overall survival in the later group (27). The POET trial which randomized patients to chemoirradiation and surgery or chemotherapy and surgery showed that neoadjuvant chemoirradiation improved 3 year survival rate from 27.7 % to 47.4 %. FFCD 9102 trial AND German Oesophageal Cancer Study Group showed that patients with squamous cell carcinoma of esophagus who are treated with chemoirradiation and achieved complete response do not benefit from additional surgery or chemotherapy. However patients with adenocarcinoma require surgical resection.

So, with the above evidences there is a good rationale to use combination of chemoirradiation and surgery and it improves survival. Definitive chemoirradiation can

be offered to those who are inoperable due to advanced disease or having comorbid conditions and patients who refuse surgery.

With these options, the patients should understand the risks and benefits of each modality especially when they have options of choosing either surgery or definitive chemoirradiation.

Each of it has its own advantages and disadvantages. It is the responsibility of the physician to outline the risks and benefits to the patient, so that he can choose the best modality of treatment.

Complications of surgery are mostly acute postoperative and the quality of life is effected mainly by the surgery related factors. Almost one in two (44%) of the patients would have had at least one major predefined complication within 30 days after surgery and 11 % of the operations were followed by more than two complications. The most frequent complications were respiratory insufficiency, severe pneumonia, anastomotic leakage, cardiac complications and serious infections. The factors which increased the risk of complications during surgery were older age, low-volume surgery, preoperative oncologic therapy, and a higher preoperative bleeding volume might increase the risk of complications, while gender and tumour stage did not play any role (37). Quality of life is of utmost importance as most of the patients who undergo surgery are also not cured (3).

Complications associated with definitive chemoirradiation include effect on esophagus as well as on surrounding tissues. Esophageal complications include esophagitis, esophageal strictures, and fistula formation. The rate of fistula formation was around 12

to 17.5 % (30,38). The rates of stricture formation is 30 – 40 % in various studies and is increased to thrice if patient receives intraluminal brachytherapy(14,16). Other complications associated with definitive chemoirradiation are pneumonitis, cardiotoxicity and hematological toxicities.

The most common causes for benign strictures of esophagus are anastomotic strictures, radiation therapy induced strictures, photodyanamic therapy for Barrett esophagus and nasogastric tube injuries. The treatment for esophageal strictures consists of dilation via bougie or balloon, steroids injection and expandable stents. Of all the above causes, radiation induced strictures are the most technicaly difficult to manage as it not only affects the lumen but also swallowing function due to damage of the swallowing muscles. These strictures are difficult to dilate and when dilatation is effective, patients still cannot swallow because of difficulty in swallowing coordination (39).

Justification of the present study

The prognosis of esophageal cancer patients is poor in spite of advancement of treatment techniques in fields of surgery or radiation therapy. Those patients who are operable at the time of diagnosis can either be treated with surgery or definitive radiation therapy as per the patient's choice. It is the responsibility of the physician to inform the patient regarding the pros and cons of each treatment modality. As the survival rates are poor, one of the main aims of any treatment modality is to improve the quality of life. Dysphagia is one such factor which decreases the quality of life in

esophageal cancer patients. This study determines the incidence rate of esophageal stenosis after definitive radiation therapy, the risk factors causing esophageal stenosis and formulates an equation which predicts the incidence of stenosis before a patient undergoes definitive radiation therapy. This study also describes the disease response rates after definitive radiation therapy.

Materials and Methods

This observational study attempts to determine the incidence and predict, the factors causing esophageal stenosis, in esophageal cancer patients who underwent chemoirradiation from January 2008 to April 2013.These patients underwent treatment in the Department of Radiotherapy Unit 1, Christian Medical College Hospital. All these patients underwent definitive radiation therapy (with external beam irradiation and intra luminal brachytherapy) with or without chemotherapy.

Inclusion Criteria:

The retrospective data includes all patients who underwent definitive irradiation with or without chemotherapy for esophageal cancer under Radiotherapy Unit I, from January 2008 to February 2013.

The prospective data included all patients who received definitive irradiation with or without chemotherapy for esophageal cancer from February 2013 till date.

The data was collected after the approval from the Institutional Review Board, Christian Medical College, Vellore.

Exclusion Criteria:

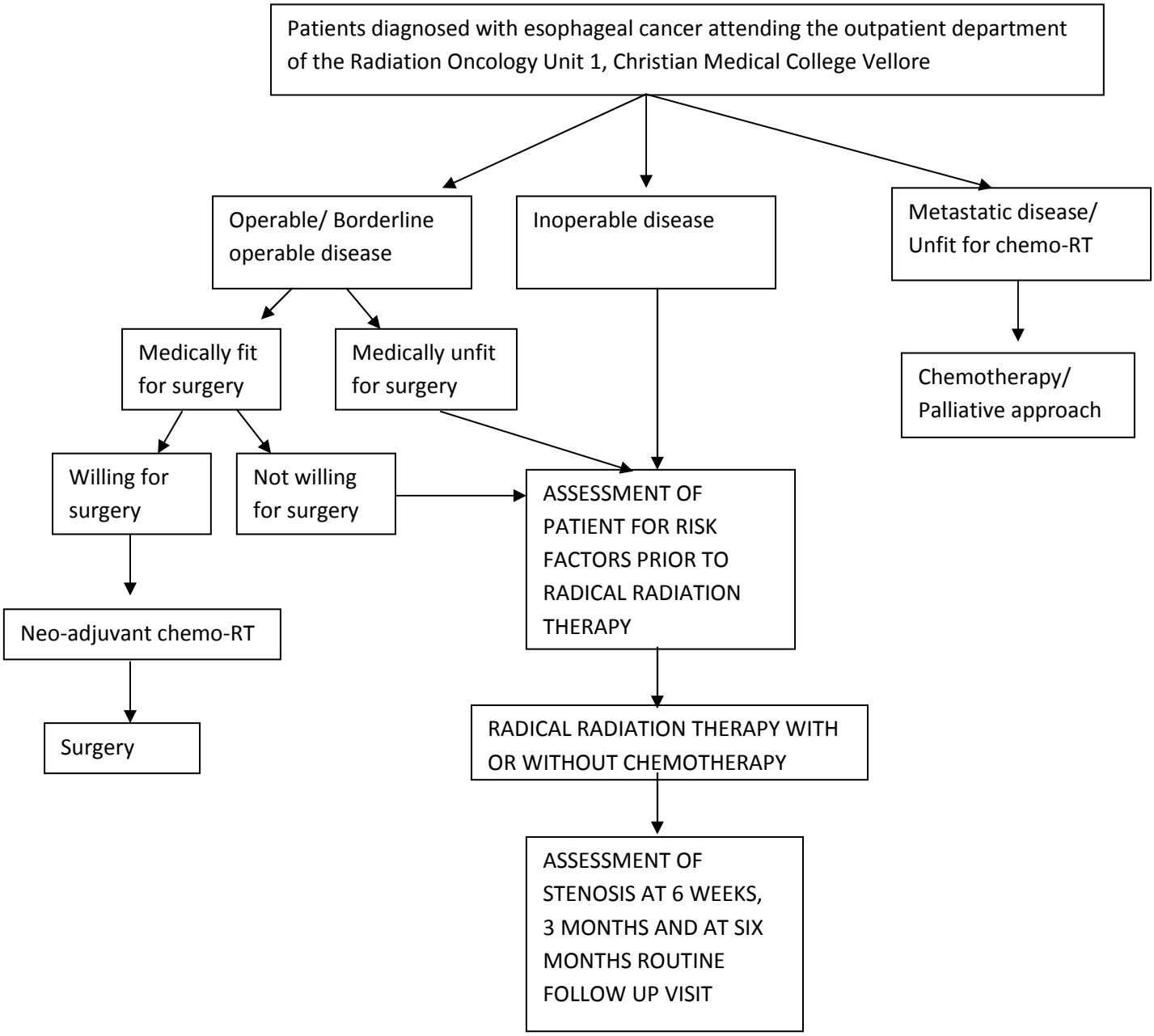
Patients who did not meet the inclusion criteria.

Evaluation:

1. Complete clinical history and examination

2. Blood counts (Hemoglobin, Total count, differential counts); Serum creatinine and liver function tests
3. Chest X ray
4. Ultrasound Abdomen
5. CT scan of the thorax
6. Upper GI scopy
7. Bronchoscopy (if indicated)

Methodology



Details of each step :

PRE TREATMENT EVALUATION

INFORMED CONSENT IN PROSPECTIVELY RECRUITED PATIENTS
BLOOD TESTS FOR CHEMOTHERAPY,
CHEST X-RAY
ULTRASOUND ABDOMEN,
ECG, ECHO AND CARDIAC ASSESSMENT
CT THORAX
UPPER GI SCOPY AND BIOPSY

ASSESSMENT OF PATIENTS PARTICIPATING IN TRAIL – AS PER THE PROFORMA

DETAILS OF RADIOTHERAPY WITH OR WITHOUT CHEMOTHERAPY

RADIATION THERAPY –CONVENTIONAL / CONFORMAL
45Gy in 25 fractions,180 cGy per fraction, 5 days per week, for a period of 5 wks
CONCURRENT CHEMOTHERAPY –ADMINSTERED WHEN PATIENT FOUND FIT.
CHEMOTHERAPEUTIC AGENTS USED:
Cisplatin/5FU
Cisplatin
Paclitaxel/Carboplatin

DETAILS OF HIGH DOSE RATE BRACHYTHERAPY

2 fractions of HDR intraluminal brachytherapy 1 wk after completion of external RT. Dose : 4.5 Gy to 0.5 cm from esophageal lumen surface in 2 fractions. Each fraction with 1 week gap

DETAILS OF POST TREATMENT EVALUATION

6 WKS, 3 MONTHS AND 6 MONTHS POST TREATMENT ASSESSMENT ========== ULTRASOUND ABDOMEN, CT THORAX UPPER GI SCOPY

Variables used in the study

There are two cohorts in the study. The first cohort is a retrospective cohort, whose data was already present in our records. The second is a prospective cohort, whose data was collected prospectively.

The main variables which were collected and thought to be a risk factor for the development of esophageal stenosis after definitive radiation therapy were

a) Tumour stage (according to TNM classification)

b) Wall thickness of esophagus prior to treatment

c) Scope negotiability through the esophagus before the initiation of treatment

d) Tumour length of esophagus

e) Circumference of the esophageal wall involved

There are no effect modifiers or confounders as all patients received definitive radiotherapy with or without chemotherapy as per the department protocol .

END POINT ANALYSIS:

- Incidence of esophageal stenosis after definitive radiation therapy
- Co-relation of esophageal stenosis with each of the variables in prediction of esophageal stenosis after definitive radiation therapy.
- To formulize an equation for prediction of esophageal stenosis based on the identified risk factors.

The characteristics of the patients who had already completed treatment were collected from the patient's outpatient & inpatient records, radiation therapy treatment records, Picture Archiving and Communication System (PACS) and gastroscopy reports.

The tumour characteristics are identified based on imaging.

a) Portion of the esophagus which was involved:

The esophageal portion which was involved by the tumour was documented both in the upper GI endoscopy as well as from the CT Thorax imaging. The portion of the esophagus involved was divided according to the AJCC anatomical division of esophagus which was given in the Cancer Staging Manual, 2007. The cervical esophagus extends from 16 to 20 cm, i.e from cricopharyngeus muscle to thoracic inlet. The upper third esophagus extends from 20 to 25 cm, i.e from thoracic inlet to tracheal bifurcation. The middle third esophagus extends from 25 to 32 cm and lower third esophagus extends from 32 to 40 cm. The anatomical regions are important in decision making of treatment of esophageal cancer. However, in some cases the Upper GI endoscope could not be negotiated beyond the growth and the entire lesion could not be assessed. So as a standard for this study CT scan of the Thorax which was taken prior to the treatment for staging purpose was considered for measurement of length of the esophagus involved. Those CT scans which did not show any thickness of the esophageal wall, i.e those which had only ulcerative lesions were measured with upper GI endoscopy.

The CT scan findings for the study were acquired with the help of one single radiologist. This was done to avoid any inter-observer variation in the interpretation of the CT scan findings.

b) T stage: The tumour was staged according to the AJCC 2010. It was documented according to the CT Thorax which was taken prior to the starting of treatment. The cohort was divided into two groups those with T4 stage and less than T4 stage.

c) Histopathology of the tumour: The biopsy which was taken from the esophageal lesion during the upper GI endoscopy was reported by the Department of the Pathology.

d) Extent of the involved circumference: This is measured from the CT scan of the Thorax. The circumference was divided into four equal quadrants and the number of quadrant involvement was documented. If the lesion was not appreciable in the CT scan, upper GI scopy report was taken into consideration. The patients were divided into those having involvement of all four quadrants (full circumference involvement) and those in whom 1 – 3 quadrants involved.

e) Tumour length: The esophageal length which was involved by tumour was measured by single radiologist from the pretreatment CT scan of the thorax. In some cases the Upper GI endoscope could not be negotiated beyond the growth and the entire lesion could not be assessed. So as a standard for this study CT scan of the Thorax which was taken prior to the treatment for staging purpose was considered for measurement of length of the esophagus involved. Those CT scans which did not show

any thickness of the esophageal wall, i.e those which had only ulcerative lesions were measured with upper GI scopy. The patients were divided into two groups, one with tumours less than 8 cm and other with tumour greater than 8 cm.

f) Wall thickness of the tumour region: This was measured from the CT scan of the Thorax. This was measured taking the maximum wall thickness of the esophagus of the tumour. The wall thickness was measured and then categorized into those which are less than 2 cm and those greater than 2 cm.

g) Stenosis Grade before treatment: Stenosis was considered to be present if the scope could not be negotiated before the treatment and no stenosis if scope was negotiable. This data was collected from the upper GI endoscopy reports done prior to starting treatment.

In the patients who were recruited prospectively, dysphagia was also graded by the patient using a validated dysphagia rating scale. The scale used was the Modified O'Rourke swallowing-status staging system. Kindly refer to [**Annexure A**].

Grading of stenosis after treatment

Stenosis after treatment was graded both subjectively and objectively. Subjectively it is measured with the modified O'Rourke swallowing status staging system. This was co-related with the dysphagia score which the patient had prior to the treatment.

Objectively, the assessment of stenosis of the esophagus was based on endoscope negotiability. It was measured using the upper GI endoscope whose diameter is 9.2 mm. For this study, stenosis was defined based on the endoscope negotiability. If the scope was negotiable, it was considered as no stenosis and if the scope is not negotiable it is considered as stenotic lesion. Stenosis could be attributed to malignancy or radiation induced stricture. The assessment is done on all follow up visits.

Table 1: Dysphagia Score based on Modified O'Rourke swallowing-status staging system

Stage Swallowing status	
1	Asymptomatic
2	Eats solids with some dysphagia
3	Eats soft or pureed food only
4	Drinks liquids only
5	No swallowing at all

Statistical Methods used for analysis of data

Calculation of the sample size:

In this cohort study, the expected rate of esophageal stenosis in the patients who received definitive radiation therapy was 50 %. Using the principle of 1 variable in a multivariate analysis for every 10 patients with the outcome of interest, the calculated sample size was 100 patients (recruited both retrospectively and prospectively).

The association between the esophageal stenosis after radiation therapy and each of the factors relating to the tumor and therapy was analyzed. The various factors which were analyzed were:

a) Tumour stage (according to TNM classification)
b) Wall thickness of esophagus prior to treatment
c) Scope negotiable through the esophagus or not
d) Tumour length of esophagus
e) Circumference of the esophageal wall involvement.

The outcome variable, stenosis, is graded according to the whether the scope is negotiable through the esophageal lumen before treatment and during each follow up visit after the treatment. In this study, the outcome was analyzed in the last follow up visit.

In consultation with the statistician, for univariate analysis, a chi-square test was performed to compare the distribution of the characteristics of patients and the treatment, among the stenosis levels. For multivariable analysis, logistic regression analysis was performed.

The study population was resampled using the bootstrapping method into large phantom samples (bootstrap samples) using computer calculations. This method estimates the magnitude of fluctuations in the mean from sample to sample and gives an idea about the sampling distribution. The resampled cohorts were then subjected to

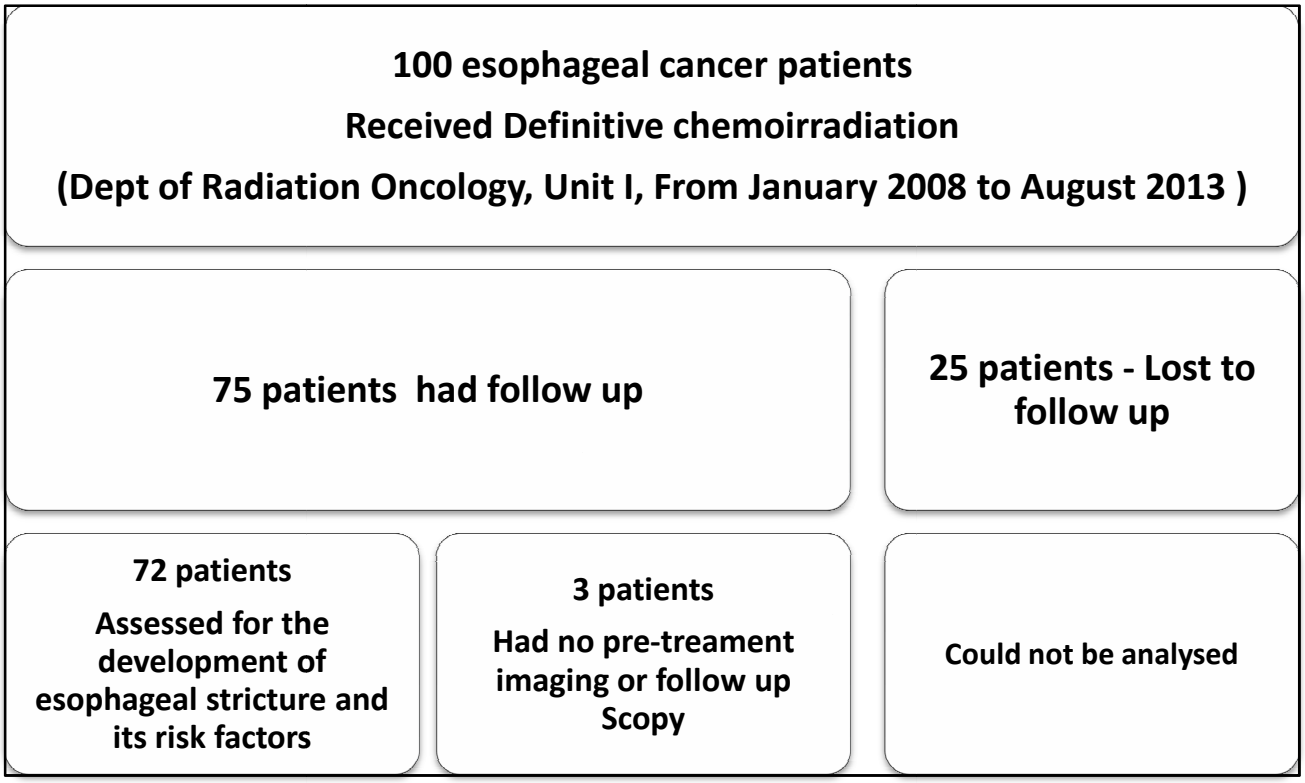
multivariate logistic regression analysis and were compared with results of the parent sample population.

The β co-efficient of each variable was calculated from the odds ratio obtained for that variable. The β co-efficient are estimates of the odds ratio between the variable and outcome when the rest of the variables are held fixed. These β coefficients were utilized in formulizing a formula for prediction of esophageal stenosis.

Results

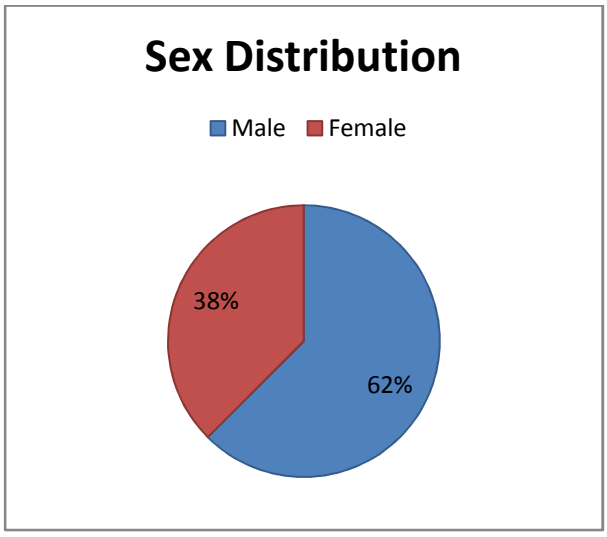
Esophageal cancer patients who received definitive radiation therapy were recruited both retrospectively and prospectively in this study. Data for 100 patients was analyzed. Of these 100, 9 patients were recruited prospectively and these patients filled the Modified O'Rourke dysphagia questionnaire. Of the 100 patients in this cohort, 28 patients had incomplete documentation or did not come for follow up to evaluate the end point of esophageal stenosis. Thus, we were able to assess 72 patients for the development of stricture after definitive radiation therapy.

Figure 1 : Study Flow chart



Patient Characteristics

There were 64 males and 36 males in the entire study group. Of the patients who were analyzed in the study 45 were males and 27 were females.



GRAPH FOR PATIENTS WHO HAD OUTCOME

The mean age of the patients was 57.56 years. The distribution of the patients for the various age groups has been shown in Fig 3.

As the histogram of the age is showing normal distribution curve, inter-quartile distributions were not calculated. There was no significant difference between the groups who had followed up and those who were lost to follow up.

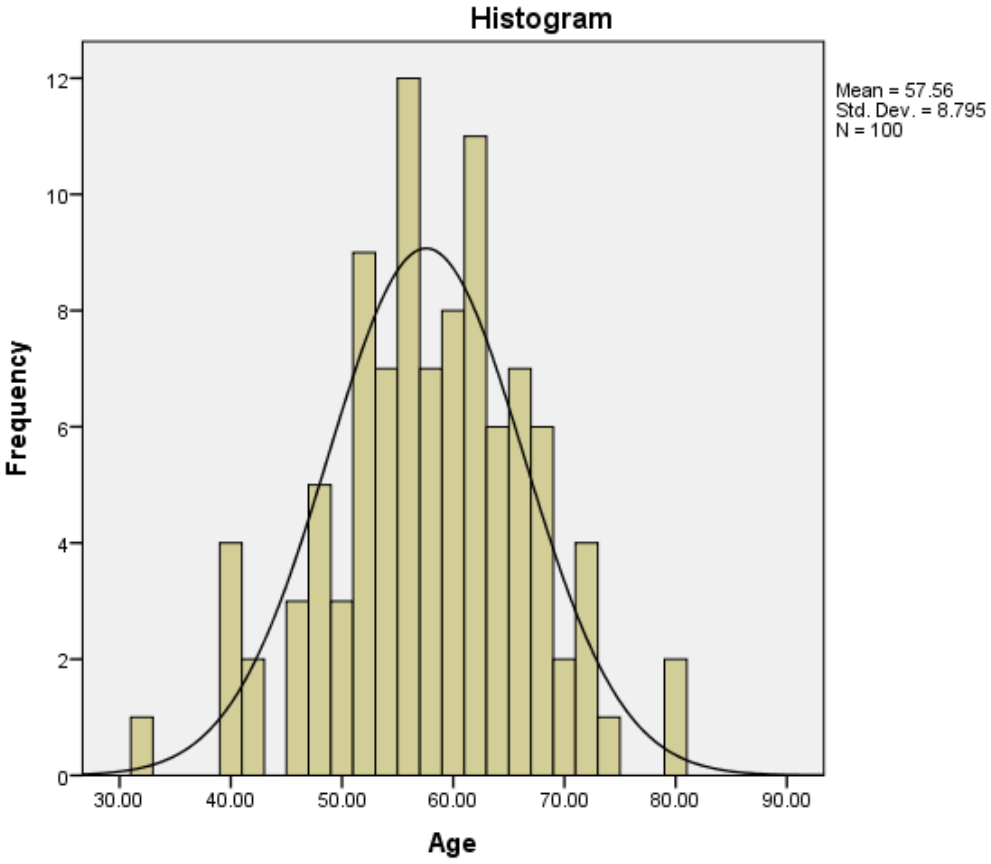


Figure 2 : AGE DISTRIBUTION

Table 2 shows the relative frequencies of patients according to different age groups.

Table 2 : Relative frequencies of Age distribution

Age in years	Frequency	Percentage	Cumulative percent
30-40	5	6.9	6.9
40-50	9	12.5	19.4
50-60	30	41.7	61.1
60-70	22	30.6	91.7
70-80	6	8.3	100
Total	72	100	

Tumour Characteristics

The tumour characteristics which were analyzed were tumour location, tumour stage (T stage), tumour length, the maximum wall thickness of the esophageal growth, circumference of the esophageal wall involved, endoscope negotiability before treatment, histopathology and peri-esophageal extension.

The particulars of the tumour characteristics are summarized in Table 3.

Table 3 : TUMOUR CHARACTERISTICS

Tumour Characteristics	No of patients			
	Without Stenosis	With Stenosis	Not Followed Up	Total No. of patients
Tumour Stage				
< T4	23	6	14	57
T4	18	25	14	43
Length of Esophagus (Involved)				
< 8 cm	35	21	24	80
>8 cm	6	10	4	20
Wall Thickness				
< 20 mm	30	21	13	64
>20 mm	11	10	15	36

Circumference Involved (No of Quadrants involved)				
1	1	0	0	1
2	2	0	1	3
3	6	1	3	10
4	31	30	23	84
Could Not be assessed	1	0	1	2
Periesophageal extension				
Present	26	26	24	76
Absent	15	5	4	24
Histopathology				
Well Diff Sq cell ca	4	2	4	10
Mod. Diff Sq cell Ca	32	23	18	73
Poor Diff Sq cell Ca	3	6	4	13
Others	2	0	2	4
Scope Negotiability (Before Rx)				
Yes	32	15	15	62
No	9	16	13	38

These patients who were included in the study underwent definitive radiation therapy with or without chemotherapy. The treatment of these patients differed in terms of

type of radiation received, total radiation dose, whether ILRT is given or not, if given what is the time gap between external beam radiation and ILRT, total duration of radiation and whether concurrent chemotherapy was administered along with radiation therapy. Table 4 gives the detailed treatment characteristics.

Table 4 : Summary of treatment Characteristics

Tumour Characteristics	No. of patients			Total No of patients
	Without stenosis	With stenosis	No follow up	
Type of Radiation	17	9	11	37
Co-60	7	7	5	19
LINAC Radical	14	13	9	36
(2D)	3	2	3	8
3DCRT				
IMRT				
Radiation Dose (EBRT)				
< 50 Gy	40	31	28	99
>50 Gy	1	0	0	1

ILRT Dose				
NIL	1	2	1	4
4.5 Gy x 1 #	3	0	1	4
4.5 Gy x 2 #	37	29	26	92
Duration of RT				
<50 days	22	12	13	47
>50 days	19	19	15	53
Time Between EBRT and ILRT				
< 7 days	9	7	8	24
>7 days	30	22	20	72
Did not receive ILRT	2	20	0	4
Concurrent Chemotherapy				
Given	32	21	23	76
Not given	9	10	5	24

These patients had a median follow up period of six months (range: 3 to 56 months). These patients were assessed for tumour response and esophageal stenosis following definitive radiation therapy with or without chemotherapy. The total number patients

who came for follow up and were included in the analysis were 72 patients. Table 5 shows the follow up data of the patients following treatment.

Table 5: FOLLOW UP DATA OF PATIENTS

Number of Patients who were analyzed				
Who came for follow up		**Lost to follow up or not analyzed**		Total
Number	***Percent***	***Number***	***Percent***	
72	72%	28	28%	100

The characteristics of patients who did not come for follow up were compared with the patients who came for follow up and were found to have no significant variation among the variables.

Characteristics	**No of patients**		
	Came for Follow up	**Did not come for follow up**	**P value**
Staging			
T4	43	14	0.378
< T4	29	14	

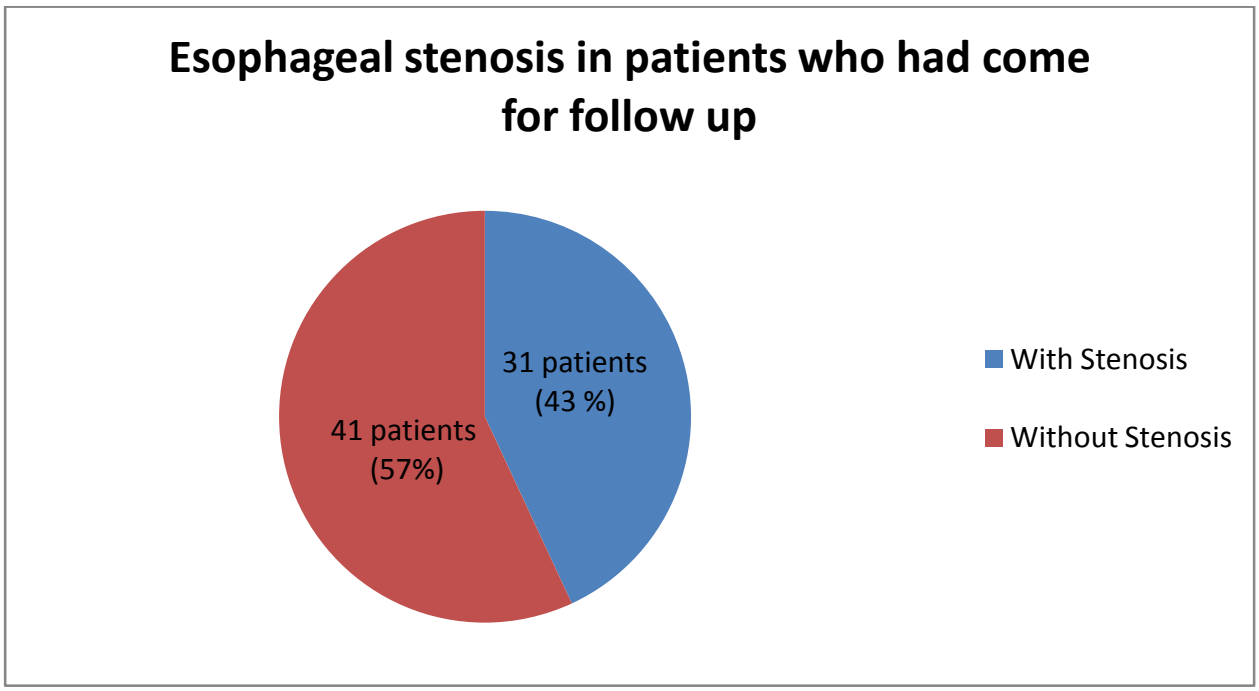
Scope negotiability before treatment			
Yes	47	15	0.279
No	25	13	
Length of the esophagus			
< 5 cm	14	1	0.095
5-10 cm	45	23	
>10 cm	13	4	
Wall thickness			
<10 mm	3	1	
10-20 mm	48	12	P = 0.072
>20 mm	21	15	

As the variables in the two groups did not differ statistically, we could interpret the results obtained in this study without any bias.

Evaluation of stenotic rates

These 72 patients were objectively assessed for esophageal stenosis during their follow up periods. 31 patients (43 %) had stenosis of esophagus following definitive radiation

therapy with or without chemotherapy and 41 patients (57%) had no stenosis. Table 4 shows the stenotic rates in the followed up patients.



Of these 31 patients who had stenosis, 12 patients had complete response, 17 patients had partial response or residual disease and 2 patients' data could not be analyzed. Of the 41 patients who had no stenosis after definitive radiation, 23 patients had complete response, 17 patients had partial response and one patient had progressive disease.

So, the incidence of stricture formation after definitive radiation was 43 % in this study and the incidence in patients who had complete response after definitive irradiation was 34 % among the stenotic group of patients.

Each of the patient, tumour and treatment related factors were co-related with the outcome of esophageal stenosis following definitive radiation therapy. In the univariate analysis, there was significant differences showed with tumour stage, stenosis level before treatment and circumference of the esophageal wall involved ($p < 0.05$). The tumour length greater than 8 cm showed a trend towards stenosis, however it was not statistically significant. Significant associations were not seen with age, gender, wall thickness, histopathology, radiation total dose, total duration of radiation, time gap between external beam irradiation and ILRT, type of radiation received and concurrent chemotherapy.

Association of stenosis with Scope negotiation prior to the treatment

The present study had shown that if scope could not be passed prior to the treatment there is a high risk of stenosis after definitive radiation therapy. In the present study, the size of scope was 9.2 mm in diameter. This study shows statistically significant difference ($p=0.009$) in incidence of stenosis in patients who had esophageal lumen less than 9 mm in diameter prior to definitive radiation therapy. Table 6 shows the cross tabulation of the stenosis of esophagus prior to treatment and its complication after treatment.

Table 6: Association of Scope Negotiation with Stricture formation

			OUTCOME		Total
			NO STENOSIS	STENOSIS	
SCOPENEG	NEGOTIABLE	Count	32	15	47
		% within OUTCOME	78.0%	48.4%	65.3%
	NOT NEGOTIABLE	Count	9	16	25
		% within OUTCOME	22.0%	51.6%	34.7%
Total		Count	41	31	72
		% within OUTCOME	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp.Sig (2-sided)
Pearson Chi- Square	6.852	1	0.009

Association of Tumour stage with stricture formation after definitive radiation therapy

The present study initially categorized patients into early esophageal (T1 and T2 stage) and late esophageal cancer (T3 and T4 stage). When this was analysed there was no statistically difference in the stenotic outcomes (p=0.225). These patients were

reclassified to those having stage T4 and those having stage less than T4. When these two groups were analyzed, there was higher stricture formation rates in stage T4, which was statistically significant (p= 0.002) when compared with the patients with less than stage T4 disease.

Table 7 shows the association of Tumour stage with Stricture formation

Table 7 : Stricture formation vs Tumour Stage

			OUTCOME		
			NO STENOSIS	STENOSIS	Total
STAGING	T4	Count	18	25	43
		% within OUTCOME	43.9%	80.6%	59.7%
	<T4	Count	23	6	29
		% within OUTCOME	56.1%	19.4%	40.3%
Total		Count	41	31	72
		% within OUTCOME	100.0%	100.0%	100.0%

Chi-Square tests

	Value	df	Asymp.Sig (2-sided)
Pearson Chi- Square	9.907	1	0.002

Association of Circumference of the esophageal wall involved and stricture formation after definitive radiation therapy

The esophageal wall was divided into four equal quadrants. The study categorized patients into those who had the tumour involving all the quadrants and those who had involvement of less than whole of the circumference. The relation between the circumference of esophageal wall involvement by the tumour and occurrence of esophageal stenosis after definitive radiation therapy was analysed and was found to be statistically significant (p=0.013).

Table 8 shows the association between the circumference of the esophageal wall involved by the tumour and formation of esophageal stenosis

Table 8 : Stenosis formation vs Circumference of the esophageal wall involved

			OUTCOME		
			NO STENOSIS	STENOSIS	Total
CIRCUMFERENCE	1-3 QUADRANTS INVOLVED	Count	11	1	11
		% within OUTCOME	24.39%	3.23%	15.28%
	ALL 4 QUADRANTS INVOLVED	Count	31	30	61
		% within OUTCOME	75.61%	96.77%	84.72%
Total		Count	41	31	72
		% within OUTCOME	100.0%	100.0%	100.0%

Chi-Square tests

	Value	df	Asymp.Sig (2-sided)
Pearson Chi- Square	6.1090	1	0.013

Association of esophageal stenosis and length of the esophageal wall involved

The patients were categorized into those having less than 8 cm of the tumour length and those having greater than 8 cm length. This was taken from the CROSS study which showed that preoperative chemoirradiation had better results than surgery alone, included the patients with tumours less than 8 cm. The present study had shown increased rates of stenosis with patients having tumour length greater than 8 cm, however it was not statistically significant (p=0.075). Table 8 shows the cross tabulation of the esophageal stenosis and tumour length (greater or lesser than 8 cm).

Table 8: Association of Tumour length with Stricture formation

			OUTCOME		
			NO STENOSIS	STENOSIS	Total
TUMOUR LENGTH	➢ 8 CM	Count	35	21	56
		% within OUTCOME	85.37%	67.74%	77.8%
	< 8 CM	Count	6	10	16

		% within OUTCOME	14.63%	32.26%	22.22%
Total		**Count**	41	31	72
		% within OUTCOME	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	Df	Asymp.Sig (2-sided)
Pearson Chi- Square	3.1723	1	0.075

Association between wall thickness and esophageal stenosis

The thickness of the esophageal wall involved by the tumour was classified into thickness of of the wall greater than 2 cm and less than 2 cm. The study did not find any statistical significant difference in the incidence of esophageal stenosis after definitve radiation therapy based on wall thickess involved by the tumour (p=0.616).

Table 9: Association between esophageal wall thickness and esophageal stenosis

			OUTCOME		
			NO STENOSIS	**STENOSIS**	**Total**
WALL THICKNESS	➢ **2 CM**	**Count**	11	10	21
		% within OUTCOME	26.83%	32.26%	29.17%

	< 2 CM	Count	30	21	51
		% within OUTCOME	73.17%	67.74%	70.83%
Total		Count	41	31	72
		% within OUTCOME	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp.Sig (2-sided)
Pearson Chi- Square	0.2518	1	0.616

Other factors did not show any co-relation with the stricture formation after definitive radiation. Table 10 shows the factors and their correlation with stricture formation.

Table 10 : Correlation of other factors with stricture formation

Characteristics	Variables used in the Study	'p' value
Periesophageal Extension	Present or Absent	0.139
Type of RT	Co-60, Linac Radical, 3DCRT, IMRT	0.721
Total Duration of RT	< 50 days or > 50 days	0.208
Interval B/w EBRT and ILRT	< 7 days, 7 or more days	0.954
Concurrent Chemotherapy	Yes or No	0.326
Histopathology	WDSCC, MDSCC, PDSCC and others	0.496

In the univariate analysis, the factors which had significant risk for the formation of esophageal stenosis following definitive radiation therapy were T4 stage tumours, scope not negotiable before initiation of treatment and tumour involving of all four quadrants of the esophageal wall. Tumours which were greater than 8 cm in length showed a trend towards increased risk of stenosis, however not statistically significant.

Multivariate analysis of various risk factors for development of Esophageal stricture formation after Definitive radiation therapy

As the sample size was only 100 with follow up patients of 72, multivariate analysis was done for 5 variables only.

Table 11 below shows the Multivariate analysis of the factors which were assessed for stricture formation after definitive irradiation.

Table 11: Multivariate analysis assessing the causative factors for stricture formation after Definitive irradiation

Variables	Univariate			Multivariate		
	OR	95% C.I	p	OR	95% C.I	P
Staging T4 <T4 (Ref)	2.31	1.34 – 3.97	0.002	1.88	1.05- 3.37	0.03
Scope negotiability Negotiable Not negotiable (Ref)	0.51	0.31 – 0.86	0.01	0.62	0.36 – 1.08	0.09

Tumour Length <8cm (Ref) >8cm	2.78	0.88 – 8.75	0.08	1.70	0.42-6.88	0.45
Wall thick <20mm (Ref) >20mm	1.29	0.47 – 3.61	0.62	0.09	0.26 – 3.11	0.88
Circumference 1-3 (Ref) 4	9.68	1.17 – 80.30	0.01	1.65	0.57 – 47.58	0.15

After multivariate logistic regression analysis, the factor which was significant was only Tumour stage 4. Scope negotiability showed a trend towards the formation of esophageal stenosis but was not statistically significant. Rest of the variables like length of the tumour, wall thickness and circumference of esophageal wall involvement had lost its significance in multivariate analysis.

The 'Goodness of Fit' for multivariate analysis was 0.70 which was not statistically significant and it suggests that the results were valid.

Tumour response at the time of last follow up

The median follow up period in these patients was 6 months (Range 3 – 56 months). The tumour response was evaluated in these patients either by CT scan of the Thorax or Upper GI endoscopy and biopsy if a suspicious lesion was present.

Out of the 72 patients who came for follow up visit, 35 patients had complete response in their first follow up period, 34 patients had partial response, 1 patient had progressed and 2 patients could not be analyzed. Figure 3 shows the graphical representation of disease follow up of the patients who came for first follow up.

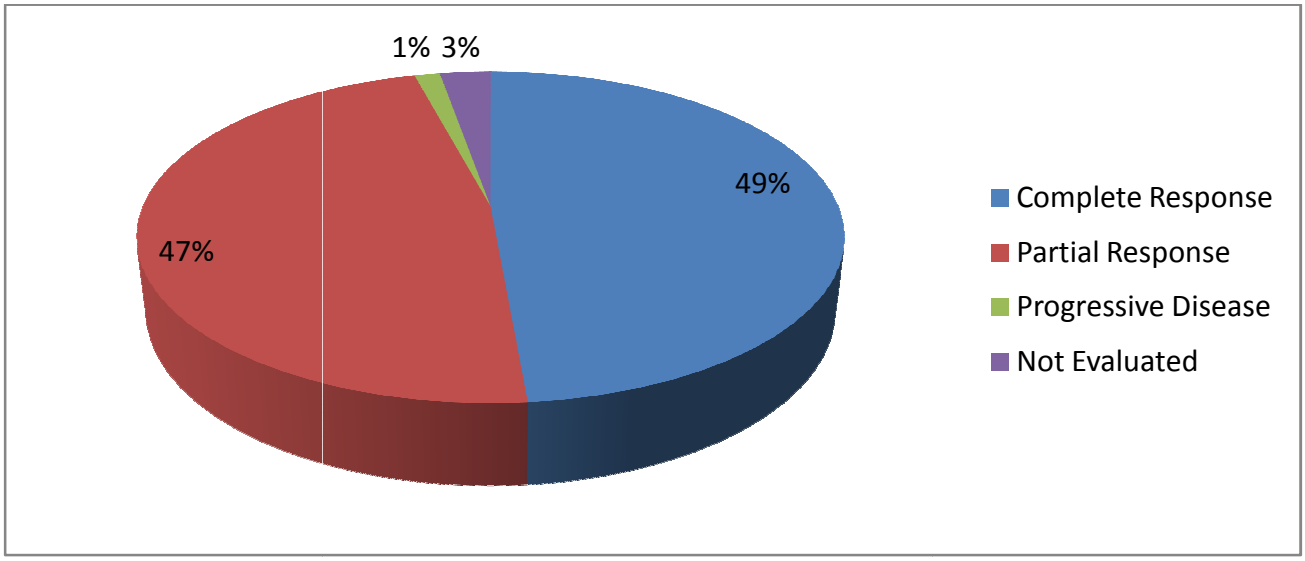


Figure 3 : Tumour response at last follow up visit

Out of the 35 patients who had complete response, 12 patients had stricture after definitive radiation therapy and 23 patients had no stricture formation. In 34 patients who had residual disease, 17 patients had stricture and 17 patients had no stricture at the time of first follow up. The patient who had progression had no stricture and he had liver metastases at the time of first follow up. Two patients whose disease status could not be evaluated had stricture formation. Table 12 shows the incidence of stricture formation after definitive radiation therapy in patients with CR, PR and PD. Table 13 shows the correlation of esophageal stenosis with the outcomes of entire cohort, i.e. those who came for follow up as well as those who did not.

Table 12: Correlational data of Stenosis rates after Definitive radiation and tumour Response at the time of Follow up

			Tumour response at follow up				Total
			CR	PR	PD	NA	
OUTCOME	NO STENOSIS		23	17	1	0	41
			56.1%	41.5%	2.4%	0.0%	100.0%
	STENOSIS		12	17	0	2	31
			38.7%	54.8%	0.0%	6.5%	100.0%
Total			35	34	1	2	72
			48.6%	47.2%	1.3%	2.6%	100.0%

CR – Complete Response, PR- Partial response, PD – Progressive Disease, NA –Could not be assessed

Table 13 : Corelational data of stenosis rates after definitive RT with response rates of entire cohort

			DiseaseFollowup				Total
			CR	PR	PD	NF	
OUTCOME	NO STENOSIS	Count	23	17	1	0	41
		% within OUTCOME	56.1%	41.5%	2.4%	0.0%	100.0%
		% within DiseaseFollowup	65.7%	45.9%	33.3%	0.0%	41.0%
	STENOSIS	Count	12	17	0	2	31
		% within OUTCOME	38.7%	54.8%	0.0%	6.5%	100.0%
		% within DiseaseFollowup	34.3%	45.9%	0.0%	8.0%	31.0%
	NOT FOLLOW UP	Count	0	3	2	23	28
		% within OUTCOME	0.0%	10.7%	7.1%	82.1%	100.0%
		% within DiseaseFollowup	0.0%	8.1%	66.7%	92.0%	28.0%
Total		Count	35	37	3	25	100
		% within OUTCOME	35.0%	37.0%	3.0%	25.0%	100.0%
		% within DiseaseFollowup	100.0%	100.0%	100.0%	100.0%	100.0%

Operability status and esophageal stenosis rates

27 out of the 100 patients were considered operable at the time of initiation of radiation in the multidisciplinary tumour board meeting. These patients however were not operated based on various reasons. 37 % of the patients (10 patients out of 27) who were operable developed stricture after radiation therapy. 11 patients had complete response after definitive irradiation. Out of the persons who were operable and had stenosis, 4 patients had complete response after definitive radiation therapy. Three patients refused surgery and 1 patient was not operated in view of advanced age (68 years).

Table 14 shows the operability status of patients at time of starting radiation therapy.

Table 14: Operability Status of patients at the time of Initiation of Radiation therapy

			Operability		Total
			OPERABLE	INOPERABLE	
OUTCOME	NO STENOSIS	Count	11	30	41
		% within Operability	40.7%	41.1%	41.0%
	STENOSIS	Count	10	21	31
		% within Operability	37.0%	28.8%	31.0%
	NOT FOLLOW UP	Count	6	22	28
		% within Operability	22.2%	30.1%	28.0%
Total		Count	27	73	100
		% within Operability	100.0%	100.0%	100.0%

Table 15 shows the operability status of the patients in relation to disease outcome.

Table 15: Operability in relation Disease Response after Definitive irradiation

			Operability		Total
			OPERABLE	INOPERABLE	
DiseaseFollowup	CR	Count	11	24	35
		% within Operability	40.7%	32.9%	35.0%
	PR	Count	9	28	37
		% within Operability	33.3%	38.4%	37.0%
	PD	Count	0	3	3
		% within Operability	0.0%	4.1%	3.0%
	NF	Count	7	18	25
		% within Operability	25.9%	24.7%	25.0%
Total		Count	27	73	100
		% within Operability	100.0%	100.0%	100.0%

Prediction formula for esophageal stenosis

The second aim of the study is to formulize an equation for prediction of esophageal stenosis prior to initiation of definitive radiation therapy. This was done using the odds ratios obtained from the multivariate analysis and the β coefficients were calculated using the formula: exp^{OR}.

Table 17 shows the odds ratios obtained from the multivariate analysis and the corresponding β coefficients.

Table 16: Odds Ratios and corresponding β coefficients

Variable	Odds Ratio (OR)	β coefficients (exp^{OR})
Staging	1.8881	0.6356
Scope Negotiation	0.6266	- 0.4674
Tumour Length	1.0705	0.5340
Wall thickness	0.9079	- 0.9655
Circumference Involved	5.1840	1.6455
Constant		-4.1435

The prediction equation is formulated using the constant obtained and the corresponding β coefficients which were obtained from the odds ratios.

Prediction equation:

Prediction equation = $\frac{e^{y}}{1+e^{y}}$, where

y = -4.1435+0.6356*staging-0.4674*scopnego+0.5340*length-0.0965*wallthick + 1.6455*circumference

e^{y} is the exponential function with a rate of change proportional to the function itself is expressible in terms of the exponential function; where e is the number also called as Napier's Number and its approximate value is 2.718281828. y is the power value of the exponent e. Based on the exponent e value 2.718281828 and raised to the power of y it has its own derivative.

The variables like staging, scope negotiability, length, wallthickness and circumference were given by the numbers assigned to them during the calculations of odds ratios.

For staging: 0– T1 to T3 stage

2 – T4 stage

For Scopenegotiability: 2 – Scope negotiable prior to starting treatment

0 – Scope not negotiable prior to treatment

For Length: 1 – If tumour less than or equal to 8 cm length

2 – If tumour more than 8 cm length

For Wall Thickness: 1 – If wall thickness less than or equal to 20 mm

2 – if wall thickness greater than 20 mm

For Circumference: 1 – 1 to 3 quadrants involved

2 – 4 quadrants are involved

After substituting the variables in the equation, the resultant value will be between 0 and 1.

If the value is 0.50 or less the likelihood of formation of stenosis is less and if the value is between 0.5 and 1, there is high chance of stenosis formation after definitive radiation therapy and value closer to 1 suggests a stronger co-relation.

This formula was derived based on the derivative cohort. However this formula needs to tested on the validation cohort when we have a sufficient larger sample.

Bootstrapping method for validation of the results

Bootstrapping is a novel technique which resamples the parent cohort multiple times and tests the validation of the results obtained from the multivariate analysis. Each of the variables tested in multivariate analysis was sampled and the validation test was repeated nearly 1000 times and results were obtained. Table 16 shows the bootstrapping statistics

After doing the bootstrapping, the tumour stage 4 and involvement of entire circumference of the esophageal wall prior to the starting of treatment were considered statistically significant.

As the bootstrapping analysis showed that T4 and involvement of all four quadrants of the esophageal wall prior to initiation of treatment resulted in esophageal stenosis which are similar variables which came as significant in univariate analysis, it suggests that the sample is uniform and the results are validated. The multivariate analysis showed that only T4 as significant in prediction of stenois, it remained statistically significant in bootstrapping method.

Table 17: Bootstrapping statistics (n=1000)

Variable	Odds Ratio	Std. Err.	Conf. Interval
Staging (T4, <T4)	1.90	0364	1.0 – 3.68
Scope negotiability Yes or No prior to RT	0.62	0.354	0.32 -1.24
Tumour length (< 8 cm or > 8 cm)	1.70	1.443	0.32 -10.79
Wall thickness (<20 mm, >20 mm)	0.90	1.369	0.17 -3.88

Circumference involved (4 quadrants, 1-3)	5.18	0.777	1.64 – 19.31

Dysphagia scores before and after definitive radiation therapy

The prospective cohort had 9 patients in whom the dysphagia scores were assessed based on their swallowing symptoms as mentioned in Annexure A. Using the prediction equation which was derived from the derivative cohort an attempt is made to predict the stenosis rates in the prospective group of patients. Table 18 shows the dysphagia scores before and after treatment as well as predictive values based on the risk factors in these patients.

Table 18 : Dysphagia scores before and after RT

S. No	Tumour Stage	Scope Negotiability	Tumour length	Wall thickness	Circumference	Dysphagia Score before RT	Dysphagia Score after RT	Stenosis after RT	Predicted Value
1	T4	No	>8 cm	< 20 mm	4	3	3 (Remained Same)	Stenosis	0.80
2	T4	Yes	>8 cm	>20 mm	4	3	2 (Improved)	Stenosis	0.59
3	<T4	No	<8 cm	>20 mm	4	4	3 (Improved)	No Stenosis	0.37
4	T4	No	>8 cm	>20 mm	4	4	5 (Worsened)	Stenosis	0.78
5	<T4	Yes	<8 cm	<20mm	3	4	3 (Improved)	No stenosis	0.04
6	T4	Yes	>8 cm	>20mm	4	2	3 (Worsened)	Stenosis	0.59
7	<T4	Yes	<8 cm	<20mm	4	3	3 (Remained Same)	Scopy not done	0.40
8	T4	Yes	<8 cm	<20mm	4	4	3 (Improved)	No stenosis	0.48
9	T4	No	<8 cm	>20mm	4	4	4 (Remained Same)	Sopy not done	0.68

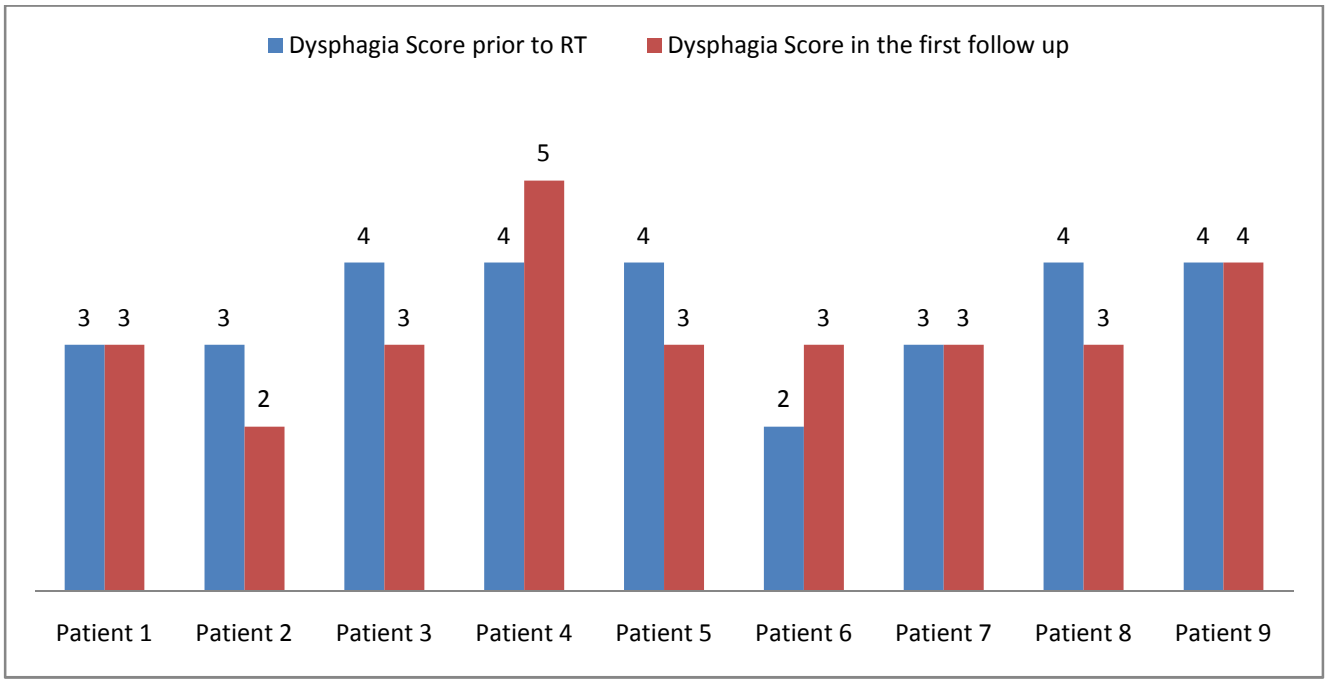


Figure 4: Comparision of Dysphagia scores before and after RT

Out of the nine patients who were assessed prospectively four patients had improved symptoms at the time of first follow up, 2 patients worsened and 3 patients had the same scores. All patients who had improved dysphagia score had scope negotiability prior to starting radiation therapy. The patients in whom the dysphagia worsened had all the risk factors present, like tumour greater than 8 cm, T4 stage, whole circumference involvement, > 20 mm wall thickness. The patients' who had worsening of dysphagia following definitive radiation therapy had stenosis of esophagus too.

By using the prediction formula, the prediction of the esophageal stenosis following definitive radiation therapy was made which was correlating with the actual outcomes.

Discussion

Esophageal cancer has a poor prognosis with five year survival rates of less than 50 % except in stage I disease. In last three decades, there has been a shift from single modality of treatment towards a multi-modality approach. RTOG 85-01 was a landmark trial which showed that definitive chemoirradiation had similar outcomes as surgery alone. RTOG 92-07 study reported that addition of ILRT after external beam radiation had improved local control but with increase late complications like strictures and fistula formation. In the present era, various trials have shown that neoadjuvant chemoirradiation followed by surgical resection have improved overall survival(27). However, in inoperable esophageal cancer, definitive chemoirradiation is one of the modality of treatment in suitable patients. At present, the survival rates of esophageal cancer are low and it is important to improve the quality of life of the patient. The pros and cons of each of treatment modality have to be known in order to provide a better quality of life for the patient. This study addressed the incidence rate and factors affecting the formation of strictures following definitive radiotherapy with or without concurrent chemotherapy.

In the present study, we had 100 patients who underwent definitive radiotherapy with or without concurrent chemotherapy. The study showed a higher incidence of esophageal cancer in males with a male to female ratio of 3:2. Similar male preponderance was shown in a study from a tertiary care centre in Tamil Nadu(40).According to the data from GLOBOCAN 2008, the male to female ratio for

esophageal cancer was 3-5:1. The mean age group of these patients was 57.6 years which was similar to the global population. Majority of the study population had squamous cell carcinoma. A study from Tamil Nadu showed a higher incidence of squamous cell carcinoma in patients who are above 40 years. The incidence rates of esophageal cancer and sex ratio distributions in the study may not be representative of the local population because patients from various parts of the country and from neighboring countries come for treatment in our institution, as tertiary care centre.

The incidence of stenosis in patients who came for follow up was 43 % (31 patients out of 72 patients). Even though 28 patients were lost to follow up, the variables studied for analysis were comparable between the two groups (those who came for follow up and those who were lost to follow up). There was no significant difference in the variables between the two groups. In RTOG 92-07, which reported the toxicity of combining the high dose rate brachytherapy with external beam irradiation in esophageal cancer, the incidence of stricture formation was 10 %. A study from India reported stricture rates of 23 % with HDR brachytherapy and external beam irradiation. Other studies which assessed the stricture rates showed the incidence of esophageal stenosis to be 20 – 30 % (14–16). Study conducted by Khurana et al reported the incidence of esophageal stenosis was increased therefore when given ILRT boost as compared to patients who received external beam radiation alone. The present study has shown a higher incidence of esophageal stenosis as compared with other studies which might be attributed to ILRT given along with external beam irradiation. But since this study did not have a comparable group with external beam irradiation alone the higher incidence

of esophageal stenosis cannot be attributed to ILRT alone. Another reason for the higher incidence of esophageal stenosis could be the method used to describe esophageal stenosis. There is no standard method for assessing post radiotherapy esophageal stenosis. Atsumi et al have compared the esophageal lumen width before and after definitive chemoirradiation with barium swallow.

In the present study, we objectively defined the esophageal stenosis with relation to scope negotiability. Dysphagia corresponds to the caliber of the stenosis; dysphagia to solids is usually present when the esophageal lumen is narrowed to 15 mm or less (3). The gastroscope used for all patients had a diameter of 9 mm thickness. We have assumed that if the scope is negotiable during the endoscopy, it was taken to be as 'no stenosis' and if not negotiable, it was considered to be ' stenosis'.

This study compared 14 variables to see if they were associated with the incidence of esophageal stenosis following definitive radiotherapy. Of the 14 variables which were analyzed , only 3 variables had a statistically significant correlation with the development of esophageal stenosis in the univariate analysis. These were T4 stage of the esophageal cancer (p=0.002), non negotiability of the gastroscope prior to the initiation of the treatment (p=0.01) and involvement of whole circumference of esophagus (p=0.04). Atsumi et al and Khurana et al have also described these variables to have a significant correlation with stenosis formation after definitive radiation. In Atsumi et al's study, other variables like tumour length and wall thickness also showed a trend towards development of esophageal stenosis. In this study, tumour length more that 8 cm in length showed a trend towards formation of esophageal stenosis but was

not statistically significant (p = 0.08). When multivariate analysis was performed only T4 tumour turned out to be statistically significant. Scope non-negotiability prior to the treatment showed a trend towards increased risk of stenosis following definitive radiotherapy. This might be due to the less number of patients and the less number of events which occurred.

The categorization of the variables into various groups was based on publications looking at similar outcomes, however with slight modifications. When T stage was categorized into early (includes T1 and T2 tumours) and late (T3 and T4 tumours), there was no significant difference in the formation of stenosis.However, when the T stage was categorized into T4 and less than T4 stage tumours, it showed a statistically significant trend in stenosis formation. Although we know T4 stage indicates poor prognosis with low chance of a cure, the quality of life after radiation therapy would remain low even after treatment with definitive radiotherapy if dysphagia persists.

Similarly, tumour length was categorized as those less than 5 cm , 5- 10 cm and greater than 10 cm which did not give any statistically significance, but when this categorization was replaced with tumour length greater than 8 cm and less than 8 cm, it showed a significant trend in the formation of esophageal stenosis in the earlier group. Larger trials which include more number of patients might have more events and therefore better validation of our prediction of dysphagia. Earlier trials which compared the complication rates with and without ILRT in patients receiving definitive radiation showed a significant increase of late complications like fistulas and strictures. We could

not study the effect of ILRT as almost all our patients received ILRT. The overall treatment time, gap between the initiation of ILRT after completion of EBRT did not show any statistically significance in the stenosis formation.

The factors which were statistically significant were validated using the bootstrapping method. This validation test showed similar outcomes as in the multivariate analysis. This method has strengthened the correlation of the variables with formation of stenosis after definitive radiation therapy.

The β coefficients were calculated using the odds ratios obtained for the each of the variables and were used in formulizing an equation for prediction of esophageal stenosis following radiation therapy. This would help in predicting the chance of the esophageal stenosis formation following definitive radiation therapy. This prediction formula accurately predicted the outcomes when tested on the prospective cohort of patients in this study. This had shown that the formula can be used for prediction of the stenosis following definitive radiotherapy. However, this formula was based on derivative cohort and needs to be tested on a larger sample to validate the equation.

Therefore, T4 stage, non-negotiability of the endoscope prior to the radiation therapy, and involvement of all quadrants of the esophageal lumen are high risk factors for the development of stenosis following definitive radiation therapy. Patients who are operable but are refusing surgery can therefore be counseled to undergo surgery if they are at a high risk for developing stenosis if they opt to undergo radiation.

Limitations of the study

1. Most of the patient data analyzed in the study were of a retrospective nature.

2. Scope negotiability was taken as an indirect parameter to assess the dysphagia in the retrospective group.

Conclusions

1. The incidence of stenosis in patients who came for follow up was 43 % (31 patients out of 72 patients).
2. The risk factors for the formation of esophageal stenosis following definitive radiation are T4 stage tumours, scope not negotiable before initiation of treatment and tumour involving full circumference of the esophageal wall.
3. Tumour length greater than 8 cm showed a trend towards increased risk of stenosis
4. A formula to predict esophageal stenosis was derived which needs to be validated on a larger data set.
5. A prospective study with a larger number of patients in whom dysphagia is assessed both by patient reported dysphagia scores as well as endoscopy and imaging would be an ideal study to predict esophageal stenosis and to validate the prediction formula derived in this study.

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ANNEXURES

ANNEXURE A

Degree of dysphagia assessment by modified O'Rourke swallowing-status staging system

Stage Swallowing status	
1	Asymptomatic
2	Eats solids with some dysphagia
3	Eats soft or pureed food only
4	Drinks liquids only
5	No swallowing at all

ANNEXURE B

PROFORMA

'A study to predict stenosis in esophageal cancer patients after definitive radiation therapy'.

Name: **Hospital No.**

Age: **Sex:**

Address:

Phone No.

Socioeconomic Status:

Performance status (ECOG):

Body Weight: **Height:**

BMI:

Smoker / Non- Smoker

Alcohol:

Symptoms:

1. **Dysphagia score**
2. **Heart burn**
3. **Rugurgitation**
4. **Chest pain**
5. **Nausea / Vomting**
6. **Cough**
7. **Odynophagia**

Dyapahagia score
1 – Asymptomatic; 2 – Eats solids with some dysphagia; 3 – Eats soft or pureed food only; 4 – Drinks liquids only; 5 – No swallowing at all

Co-morbidities:

Cardiac / Pulmonary / Renal / Hepatic / Diabetes

<u>Investigation</u> –

Gastroscopy :

Location :

Length of the lesion :

Type of lesion : 1. Polypoid
2. Ulcerative
3. Stricture

Circumference extent :

1. <25 % 2. 25 – 50 % 3. 50 -75 % 4. >75 %

Scope Negotiation prior to RT : Negotiation : Yes /No

Feeding Procedure : NG tube - Y/N
PEG - Y/N

Imaging :

CT / PET CT scan

Location :

Length of the lesion - 1. < 5 cm 2. 5 - 10 cm 3. > 8 cm

Wall thickeness - 1. < 10 mm 2.10 – 20 mm 3. > 20 mm

Periesophageal extension

Intraluminal extension

Nodes - Y/N

Distant Metastases

Stage :

T N M

Histology :
Biopsy No :

Treatment :

Neoadjuvant chemotherapy : Y/N

Type of chemotherapy

Number of cycles

Response to Neoadjuvant chemotherapy:

Radiology report : CR PR SD PD

Gastroscopy

Radiation therapy details :

1. **Conventional 2. Conformal**

   Dose :

   Intraluminal Brachytherapy : Y / N

   Dose

   Total Duration of RT
   1. 6 weeks 2. 6-7 weeks 3. > 7 weeks

   Time between EBRT and ILRT
   1. < 7 days 2. > 7 days

Concurrent Chemotherapy : Y /N

Chemotherapy Drug :

1. **Cisplatin + 5 FU**
2. **Weekly Cisplatin**
3. **Cisplatin 3 weekly**
4. **Docetaxel**
5. **Paclitaxel and Carboplatin**

Number of cycles

Follow up after RT :

	1st - 6 weeks	**2nd – 3 months**	**3rd – 6 months**
Date			
Dysphagia Score			
Radiology			
Gastroscopy- Scope Negotiability			

ANNEXURE C

Patient's Information sheet

Christian Medical College, Vellore

Department of Radiation therapy

Study Title: A study to predict stenosis in esophageal cancer patients after definitive radiation therapy.

You are being requested to participate in a study which aims to identify the risk factors which can predict the narrowing of food pipe after treatment with radiation therapy and chemotherapy. This might help us in identifying the risk factors and also in predicting the narrowing of the food pipe after treatment on an individual basis. This study may help us to select the ideal type of treatment being offered to a patient based on the risk factors which are present.

What does this study do?

In this study we will collect data from your previous records like OP charts, RT charts or from the clinical workstation of CMC Vellore.

New patients who are yet to undergo treatment for esophageal cancer will be asked to fill up a questionnaire form related to difficulty in swallowing.

Does this study have any side effects?

This study collects only data of the patients from patient records ,investigations and a questionnaire. Therefore, there is no risk of any side effects.

If you take part what will you have to do?

If you agree to participate in this study, you will be given a swallowing assessment score questionnaire form to be filled up before your treatment and also in the subsequent routine follow up visits at 6 weeks, 3 months and six months.

All other treatments that you are already on will be continued and your regular treatment will not be changed during this study. No additional procedures or blood tests will be conducted for this study.

Can you withdraw from this study after it starts?

Your participation in this study is entirely voluntary and you are also free to decide to withdraw permission to participate in this study. If you do so, this will not affect your usual treatment at this hospital in any way.

What will happen if you develop any study related injury?

Since this is an observational study, there is no study related injury.

Will you have to pay for the study?

No

What happens after the study is over?

You will be advised to have regular checkups at the specified intervals as advised by your treating doctor.

Will your personal details be kept confidential?

If you participate, your reports may be made available to the researchers involved in this study at the Christian Medical College, Vellore. This information may include:

- Test results (lab work, x-rays, Gastroscopy, CT or MRI scans, body scans and any other tests you have had)
- Details about your treatment outcome

No record bearing your name will be provided to anyone else except the investigators involved in this study. You will not be identified as an individual in any report coming from this study.

All data obtained from this study will be stored and may be used for future analysis without obtaining further consent from you.

If you have any further questions, please ask Dr. Venkata Krishna Reddy , Ph No : 09751875557 , email: drkrishna@cmcvellore.ac.in

ANNEXURE D

INFORMED CONSENT

Study Title: A study to predict stenosis in esophageal cancer patients after definitive radiation therapy.

Study Number:

Participant's name:

Date of Birth / Age (in years):

I_____

_____, son/daughter of _____

(Please tick boxes)

Declare that I have read the information sheet provide to me regarding this study and have clarified any doubts that I had. [ ]

I also understand that my participation in this study is entirely voluntary and that I am free to withdraw permission to continue to participate at any time without affecting my usual treatment or my legal rights [ ]

I understand that the study staff and institutional ethics committee members will not need my permission to look at my health records even if I withdraw from the trial. I agree to this access [ ]

I understand that my identity will not be revealed in any information released to third parties or published [ ]

I voluntarily agree to take part in this study [ ]

Name:	Name of witness:
Signature:	Relation to participant:
Date:	Date:

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Chairperson, Research Committee & Principal

Dr. Nihal Thomas
MD,MNAMS, DNB(Endo), FRACP(Endo), FRCP(Edin)
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

Ref: IRB-A1-13.02.2013

February 18, 2013

Dr. Venkata Krishna Reddy
PG Registrar
Department of Radiation Oncology
Christian Medical College
Vellore 632 004

Ref: IRB Min No: 8055 dated 06.11.2012

Dear Dr. Venkata Krishna Reddy,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed the following document 1. Request to include additional co investigator – Dr. B. Antonisamy, Professor, Biostatistics for the study titled "A study to predict stenosis in esophageal cancer patients after definitive chemoirradiation" on February 13, 2013.

Name	Qualification	Designation	Other Affiliations
Dr. Susanne Abraham	MBBS, MD	Professor, Dermatology, Venerlogy & Leprosy, CMC.	Internal, Clinician
Dr. Benjamin Perakath	MBBS, MS, FRCS	Professor, Surgery (Colorectal), CMC.	Internal, Clinician
Dr. Ranjith K Moorthy	MBBS MCh	Professor, Neurological Sciences, CMC	Internal, Clinician
Dr. P. Prasanna Samuel	B.Sc, M.Sc, PhD	Professor Dept. of Biostatistics, CMC	Internal, Statistician
Dr. Balamugesh	MBBS, MD(Int Med), DM, FCCP (USA)	Professor, Dept. of Pulmonary Medicine, CMC.	Internal, Clinician

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Dr. Nihal Thomas
MD,MNAMS, DNB(Endo), FRACP(Endo), FRCP(Edin)
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

Dr. Simon Rajaratnam	MBBS, MD, DNB (Endo), MNAMS (Endo), PhD (Endo), FRACP	Professor, Endocrinology, CMC	Internal, Clinician
Dr. Anup Ramachandran	PhD	The Wellcome Trust Research Laboratory Gastrointestinal Sciences	Internal
Dr. Chandrasingh	MS, MCH, DMB	Urology, CMC	Internal, Clinician
Dr. Paul Ravindran	PhD, Dip RP, FCCPM	Professor, Radiotherapy, CMC	Internal
Dr. Vathsala Sadan	M.Sc, Ph.D	Addl. Deputy Dean, College of Nursing, CMC.	Internal, Nurse
Dr. Ellen Ebenezer Benjamin	M.Sc	Maternity Nursing, CMC	Internal, Nurse
Dr. Denny Fleming	BSc (Hons), PhD	Honorary Professor, Clinical Pharmacology, CMC.	Internal, Pharmacologist
Dr. Priya Abraham	MBBS, MD, PhD	Professor, Virology, CMC	Internal, Clinician
Dr Ashok Chacko	MD, DM, FRCP, FRCPG, FIMSA, FAMS	Director, Institute of Gastroenterology and Liver Disease, Madras Mission, Chennai	External, Clinician
Dr. Anand Zachariah	MBBS, MD, DNB	Professor, Dept. of Medicine, CMC	Internal, Clinician
Mrs. Pattabiraman	BSc, DSSA	Social Worker, Vellore	External, Lay Person
Mr. Sampath	BSc, BL	Advocate	External, Legal Expert
Mr. Harikrishnan	BL	Lawyer, Vellore	External, Legal Expert

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Mr. Samuel Abraham	MA, PGDBA, PGDPM, M.Phil, BL	Legal Advisor, CMC.	Internal, Legal Expert
Mr. Joseph Devaraj	BSc, BD	Chaplain, CMC	Internal, Social Scientist
Dr. B. J. Prashantham (Chairperson), IRB Blue Internal	MA (Counseling), MA (Theology), Dr Min(Clinical	Chairperson(IRB)& Director, Christian Counselling Centre	External, Scientist
Dr. Jayaprakash Muliyil	BSC, MBBS, MD, MPH, DrPH(Epid), DMHC	Retired Professor, Vellore	External, Scientist
Dr. Nihal Thomas	MD MNAMS DNB(Endo) FRACP(Endo) FRCP(Edin)	Secretary IRB (EC)& Dy. Chairperson (IRB), Professor of Endocrinology & Addl. Vice Principal (Research), CMC.	Internal, Clinician

We approve the above documents as presented.

Yours sincerely,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr Nihal Thomas
MBBS MD MNAMS DNB (Endo) FRACP(Endo) FRCP(Edin)
Secretary (Ethics Committee)
Institutional Review Board

TEL : 0416 - 2284294, 2284202 FAX : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

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Additional Vice Principal (Research)

January 24, 2013

Dr. Venkata Krishna Reddy P
PG Registrar
Department of Radiation Oncology
Christian Medical College
Vellore 632 002

Sub: **FLUID Research grant project NEW PROPOSAL:(RESUBMISSION)**
A study to predict stenosis in esophageal cancer patients after definitive chemoirradiation.
Dr. Venkata Krishna Reddy P, Radiation Oncology, Dr. Simon Pradeep Pavamani, Dr. Selvamani,Radiation Oncology- I, Dr. A J Joseph, Dr. Reuben Thomas Kurien, Gastroenterology, Dr. Sridhar Gibikote, Radiology.

Ref: IRB Min. No. 8055 dated 06.11.2012

Dear Dr. Venkata Krishna Reddy P,

I enclose the following documents:-

1. Institutional Review Board approval
2. Agreement

Could you please sign the agreement and send it to Dr. Nihal Thomas, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Alfred Job Daniel
Principal & Chairperson (Research Committee)
Institutional Review Board

Chairperson (Research Committee) &
Principal
Christian Medical College
Vellore - 632 002, Tamil Nadu, India.

CC: Dr. Simon Pradeep Pavamani, Department of Radiation Oncology

TEL : 0416 - 2284294, 2284202 FAX : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

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Ref: IRB Min. No. 8055 dated 06.11.2012

Dear Dr. Venkata Krishna Reddy P,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "A study to predict stenosis in esophageal cancer patients after definitive chemoirradiation." on November 6, 2012.

The Committees reviewed the following documents:

1. Format for application to IRB submission
2. Information Sheet and Consent Form (English, Tamil and Telugu)
3. Cvs of Drs. Venkata Krishna Reddy, Simon Pradeep Pavamani, Selvamani, A J Joseph,. Reuben Thomas Kurien, Sridhar Gibikote
4. A CD containing documents 1 - 3

The following Institutional Review Board (Research & Ethics Committee) members were present at the meeting held on November 6, 2012 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

INSTITUTIONAL REVIEW BOARD (IRB)
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Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

Name	Qualification	Designation	Other Affiliations
Dr. Priya Abraham	MBBS, MD, PhD	Professor, Virology, CMC	Internal, Clinician
Dr. Srinivasa Babu	M.Sc, M.Phil, PhD	Sr. Scientist, Neurological Sciences, CMC	Internal, Clinician
Dr. Susanne Abraham	MBBS, MD	Professor, Dermatology, Venerlogy & Leprosy, CMC.	Internal, Clinician
Dr. Bobby John	MBBS, MD, DM, PHD, MAMS	Cardiology, CMC	Internal, Clinician
Dr. Denny Fleming	BSc (Hons), PhD	Honorary Professor, Clinical Pharmacology, CMC.	Internal, Pharmacologist
Dr. Simon Rajaratnam	MBBS, MD, DNB (Endo), MNAMS (Endo), PhD (Endo FRACP	Professor, Endocrinology, CMC	Internal, Clinician
Dr. Ranjith K Moorthy	MBBS MCh	Professor, Neurological Sciences, CMC	Internal, Clinician
Dr. Anup Ramachandran	PhD	The Wellcome Trust Research Laboratory Gastrointestinal Sciences	Internal
Dr. Chandrasingh	MS, MCH, DMB	Urology, CMC	Internal, Clinician
Dr. Benjamin Perakath	MBBS, MS, FRCS	Professor, Surgery (Colorectal), CMC.	Internal, Clinician
Dr. Vinitha Ravindran	M.Sc Nursing, PhD	Professor, Child Health Nursing, CMC.	Internal, Nurse
Mrs. S. Pattabiraman	BSc, DSSA	Social Worker, Vellore	External, Lay Person
Mrs. Mary Johnson	M.Sc	Professor, Child Health Nursing, CMC.	Internal, Nurse
Mr. Harikrishnan	BL	Lawyer, Vellore	External, Legal Expert
Mr. Sampath	BSc, BL	Advocate	External, Legal Expert

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We approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any serious adverse events occurring in the course of the project, any changes in the protocol and the patient information/informed consent. And on completion of the study you are expected to submit a copy of the final report.

A sum of Rs 4,500/- (Rupees four thousand five hundred only) will be granted for 12 months.

Yours sincerely

Dr. Alfred Job Daniel
Principal & Chairperson (Research Committee)
Institutional Review Board

Chairperson (Research Committee) &
Principal
Christian Medical College
Vellore - 632 002, Tamil Nadu, India

CC: Dr. Simon Pradeep Pavamani, Department of Radiation Oncology

TEL : 0416 - 2284294, 2284202 FAX : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

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Introduction Esophageal cancer is the eighth most common cancer worldwide. It is more common in males, with male to female ratio of 3-5:1. The main symptoms with which esophageal cancer patients present with are dysphagia, weight loss, heart burn, odynophagia and shortness of breath. Of these symptoms, dysphagia is the main symptom responsible for decreasing the quality of life. The mortality rate among the esophageal cancer patients despite radical treatment is high. The two and five year overall survival rates are 24.3 % and 13.8 % respectively(1). As the overall survival rates in esophageal cancer patients are low, one of the main intent of treatment in these patients is improving the...

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